VA RESEARCH ON ALZHEIMER'S DISEASE, PARKINSON'S DISEASE, AND DIABETES

HEARING

BEFORE THE

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OF THE

COMMITTEE ON VETERANS' AFFAIRS

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VA RESEARCH ON ALZHEIMER'S DISEASE, PARKINSON'S DISEASE, AND DIABETES

WEDNESDAY, APRIL 28, 2004

U.S. HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
COMMITTEE ON VETERANS' AFFAIRS,
Washington, DC

The subcommittee met, pursuant to notice, at 10 a.m., in room 334, Cannon House Office Building, Hon. Steve Buyer (chairman of the subcommittee) presiding.

Present: Representatives Buyer, Hooley, Evans, Boozman, and Udall.

OPENING STATEMENT OF CHAIRMAN BUYER

Mr. BUYER. Good morning.

The Subcommittee on Oversight and Investigations of the Committee on Veterans' Affairs will come to order.

Today's VA hearing of this subcommittee will focus on the VA research on Alzheimer's disease, Parkinson's disease, and diabetes.

The date is April 28, 2004.

By way of opening, I would like to commend the President.

Yesterday he was in Baltimore, and his proposal to provide 100 million in IT grants is welcomed. It is an important step in advancing the electronic medical records. Electronic medical records will increase patient safety, provide cost savings, and ensure greater efficiencies.

This subcommittee has held numerous hearings on this issue, and I believe that the VA can be at the forefront of leading our medical industries with IT and how we can best serve patients in this country.

I have not had the opportunity to read the President's executive order that he signed in its entirety here. I look forward to reading it after the hearing. The executive order regards the incentives for the use of information technology in establishing a position of the National Health Information Technology Coordinator, and this is a very, very good initiative, and the President not only looking to the VA but then turning to Health and Human Services to begin to move the country to the forefront and utilize technologies.

This is a good thing.

Today's hearing will review biomedical research being conducted by the VA and the NIH on Alzheimer's disease, Parkinson's disease, and diabetes. It will also provide us with an opportunity to learn about collaborative efforts between the VA and NIH in these fields of research.

I think most of us have the same questions when the subject of Alzheimer's, diabetes, and Parkinson's is brought up. I believe we would all like to know what are the root causes of these diseases, what are the risk factors in developing these diseases, and what treatments are available.

Many of us in this room have family members or know friends or neighbors or colleagues afflicted by these life-changing diseases.

The VA and NIH have been making tremendous strides in these areas. For instance, several generic markers have been identified for Alzheimer's, but the cause of the disease is still unknown.

Alzheimer's may be genetic in nature. In fact, three major genes for early onset AD and one of the major risk factors genes of late onset AD have been identified.

Other possible links include elevated levels of certain amino acids called homocysteine, and inflammation in the brain.

In the case of Parkinson's disease, many researchers believe that the combination of oxidative damage, environmental toxins, genetic predispositions, and accelerated aging are responsible for the development of this disease.

Researchers are still searching for the cause or causes of diabetes. While Type 1 diabetes usually occurs in childhood and adolescence, it is also found in adults. Type 2 diabetes, usually associated with older, overweight individuals, is now also manifesting itself in young adults and children.

Treatment of Type 1 diabetes is through daily insulin injections. Type 2 diabetes is usually monitored and treated through diet and exercise and in some case with a combination of diet, exercise, and medication.

Approximately 4.5 million Americans are estimated to have Alzheimer's, and the VA treated approximately 103,800 veterans with Alzheimer's in 2003. Alarmingly, the number of people with Alzheimer's is projected to rise to 7 million by 2020 and 14 million by 2050.

Thenational cost of Alzheimer's disease is estimated to be in excess of $100 billion. AD is the eighth leading cause of death in the United States, 53,852 in 2001, the latest statistics that were available from CDC.

Diabetes affects more than 18 million and is the sixth leading cause of death, in excess of 200,000 individuals per year. The estimatednational cost of diabetes to our society is $132 billion a year.

Parkinson's disease strikes about 50,000 people a year. The total number of people afflicted with Parkinson's is estimated to be between 500,000 to 1 million. It is estimated that 42,000 veterans suffer from Parkinson's. The cost to the Nation is estimated in excess of $5.6 billion annually.

At the present time, there is no cure for any of these diseases. Treatment is also limited, and many of the medications given to alleviate the symptoms often have serious side effects.

I look forward to hearing from our witnesses about the research being conducted by the departments and any new developments in these specific areas of research.

One of the areas that I am most hopeful to hear from the witnesses is that the Congress is beginning to be more focused on pre-

vention rather than treatment on the back end. So, I am most hopeful that we can have part of that discussion here today.

At this time, I will yield to the ranking member for any comments she may have.

Ms. Hooley, you are now recognized.

OPENING STATEMENT OF HON. DARLENE HOOLEY

Ms. HOOLEY. Thank you, Mr. Chair.

I am pleased that this subcommittee will hear testimony today regarding the progress of treating Parkinson's, Alzheimer's, and diabetes. As our chairman said, I think we all know family and friends that have been diagnosed with one of these diseases, and I know my mother, who died of cancer, the disease she was most afraid of was Alzheimer's.

Our witnesses represent some of the brightest leaders in research on this subject of anywhere in the world. So I am very excited to hear what you have to say today. Thank you for being here and informing this subcommittee of both your progress and your prognosis for the future regarding these diseases.

I understand that some collaborative research involves VA medical centers and utilizes staff facilities and patients from the Department of Veterans Affairs. I also understand that these collaborative efforts have yielded state-of-the-art treatments, treatments that may substantially reduce the potential devastating impact of these debilitating diseases.

My home state of Oregon is host to a collaborative research effort involving the Oregon Health Science University and the Portland VA Center and other institutions to create a Center of Excellence in Oregon to improve care for people with Parkinson's disease. The Parkinson's Center of Oregon is anationally recognized leader in a broad spectrum of research on Parkinson's and related neurological disorders.

The Oregon Center and other Parkinson's centers of excellence investigate the effects of various treatment methods involving medication, mobility, exercise, training, and surgery-based solutions that provide deep brain stimulation.

Diabetes is characterized in witness statements as a major and escalating public health problem affecting some 18 million Americans. It is a problem with cost—financial cost, human cost. One in every six veterans has diabetes. Its prevalence in the general population is growing at an alarming rate. In two decades, one-tenth of our population will be afflicted.

VA must be ready for increasing numbers of patients with the disease in the out-years, anticipating that those patients will place an increased burden on our resources.

Beyond necessitating lifestyle change in those who are afflicted, the disease carries with it an increased risk of coronary artery disease and stroke, as well as microvascular complications that may result in blindness or amputation.

Alzheimer's disease is also growing in prevalence in the United States general population as it gains longevity. Alzheimer's begins with mild memory loss and progresses until even simple tasks cannot be performed. Alzheimer's changes the wiring in the brain

through an inexorable buildup of plaques and tangles which result in the loss of connections among nerve cells involved with memory.

Currently, about 4.5 million people have Alzheimer's. Forecasts paint a bleak future if remedies are not found.

Research has yielded an increased understanding of disease mechanisms for each topic area at today's hearings. I look forward to hearing what's been accomplished in each area and what the future holds.

Thank you, and I yield back.

Mr. BUYER. Mr. Udall, would you like an opening statement?

Mr. UDALL. Yes. Thank you, Mr. Chairman.

Mr. BUYER. You are now recognized.

OPENING STATEMENT OF HON. TOM UDALL

Mr. UDALL. I would like to thank the chairman and ranking member for holding a hearing on this important topics.

Alzheimer's, Parkinson's, and diabetes strike a very personal chord for millions of Americans, including me. My uncle, Morris Udall, affectionately known by many members of Congress as "Mo," was diagnosed with Parkinson's disease in 1979, after serving as a member of the House of Representatives for 18 years. Even after his diagnosis, he remained an active Member of Congress until 1991.

In 1997, the President signed a bill called the Morris K. Udall Parkinson's Disease Research Act, which helped establish 11 Udall Centers of Excellence for Parkinson's disease research at medical institutions around the country. These centers conduct research in an effort to improve diagnosis and treatment of those with Parkinson's and other neurodegenerative disorders.

I have seen firsthand the devastating effects of this disease. I know the hardships it causes for 50,000 Americans who are diagnosed with Parkinson's each year. The approximately 42,000 veterans who suffer from Parkinson's need to know that NIH and the VA are doing—what they are doing to research this condition and to work towards a cure.

I look forward to hearing from our panelists on this topic. I also look forward to hearing from our panelists about efforts to combat Type 2 diabetes in veterans and in the general population.

The figures showing how much this disease costs the Nation each year, approximately 132 billion, are startling. Educating our Nation on preventive health measures and helping those who are most at risk of this disease is critical on many levels.

I think we all agree that health care for our Nation's veterans should be the best of the best. This hearing presents the perfect opportunity to flesh out how this goal is being accomplished through the NIH and the VA and the collaboration between them, and I thank you, Mr. Chairman, and yield back.

Mr. BUYER. Ranking member of the full committee for an opening statement, Mr. Evans, you are now recognized.

OPENING STATEMENT OF HON. LANE EVANS

Mr. EVANS. Thank you, Mr. Chairman.

I, along with 500,000 of my fellow Americans, live with Parkinson's every day. I personally understand the challenge of physical

activities that once were second nature. I used to play basketball in the old days.

I commend the VA's initiation and implementation of six specialized research areas. VA has partnered with these agencies to create centers of excellence for Parkinson's and many other diseases, as well.

As the veteran population gets older, it is important the VA target the age-specific issues we have before us today. Research holds the promise that a cure exists for victims of those diseases and that a cure is just over the horizon.

I will vouch for the fact that there are significant quality of life issues at stake in achieving a cure.

Mr. Chairman, again, I appreciate your holding this hearing and look forward to working with you on these issues and others in the near future.

Thank you very much.

Mr. BUYER. Thank you, Mr. Evans. You are a living reminder and example to a lot of us of having to go through Parkinson's, and no differently than Mr. Udall's uncle, who ended up here in a VA hospital and was well cared for here in Washington, DC.

We are really proud of you, Lane, because your mind is as sharp as it was on the basketball court and as it was as a United States Marine, but the body is not keeping up, and the more we are able to learn about the human physiology and the body, it is extremely important. We are proud of you for sustaining yourself in an institution that can be very difficult and highly dynamic. You are a good reminder to a lot of us that our bad day is really one of your good days, and I am proud of you for that. I am glad you are here today, and you will be an excellent participant in this hearing today.

Dr. Salerno, I am going to open up by saying I am also very proud of you.

Anybody that can go through Harvard and then take on a commission and serve as a lieutenant commander—you are a mentor to many Harvard graduates, some of whom I know, and I will yield to you first—only Dr. Kussman, because she pulls rank on you, too, but please, Dr. Salerno, you are now recognized for an opening statement.

If you have a written statement, it shall be entered into the record.

You are now recognized for five minutes.

STATEMENTS OF JUDITH A. SALERNO, M.D., DEPUTY DIRECTOR, NATIONAL INSTITUTE ON AGING, NATIONAL INSTITUTES OF HEALTH, ACCOMPANIED BY DIANE D. MURPHY, PROGRAM DIRECTOR, NEURODEGENERATION, NATIONAL INSTITUTE ON NEUROLOGICAL DISORDERS AND STROKE, NATIONAL INSTITUTES OF HEALTH; JUDITH FRADKIN, M.D., DIRECTOR, DIVISION OF DIABETES, ENDOCRINOLOGY AND METABOLIC DISEASES, NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES, NATIONAL INSTITUTES OF HEALTH; MARCELLE MORRISON-BOGORAD, ASSOCIATE DIRECTOR, NEUROSCIENCE AND NEUROPSYCHOLOGY OF AGING PROGRAM, NATIONAL INSTITUTE ON AGING, NATIONAL INSTITUTES OF HEALTH; MICHAEL J. KUSSMAN, M.D., ACTING DEPUTY UNDER SECRETARY FOR HEALTH, VETERANS HEALTH ADMINISTRATION, DEPARTMENT OF VETERANS AFFAIRS, ACCOMPANIED BY TIMOTHY J. O'LEARY, M.D., DIRECTOR, BIOMEDICAL LABORATORY R&D SERVICES, OFFICE OF CHIEF RESEARCH AND DEVELOPMENT OFFICER, VETERANS HEALTH ADMINISTRATION, DEPARTMENT OF VETERANS AFFAIRS; FRANKLIN J. ZIEVE, M.D., ASSOCIATE CHIEF OF STAFF FOR RESEARCH, RICHMOND VA MEDICAL CENTER, DEPARTMENT OF VETERANS AFFAIRS; ROBERT J. FERRANTE, DIRECTOR, EXPERIMENTAL NEUROPATHOLOGY PROGRAM, GERIATRIC RESEARCH, EDUCATION AND CLINICAL CENTER, BEDFORD VA MEDICAL CENTER, DEPARTMENT OF VETERANS AFFAIRS; AND MARY SANO, ASSOCIATE CHIEF OF STAFF FOR RESEARCH, BRONX VA MEDICAL CENTER, DEPARTMENT OF VETERANS AFFAIRS

STATEMENT OF JUDITH A. SALERNO

Dr. SALERNO. Thank you.

Thank you, Chairman Buyer.

I am pleased to be here today to discuss three conditions of great importance to the health and well-being of millions of Americans—Alzheimer's disease, Parkinson's disease, and diabetes.

I am deputy director of the National Institute on Aging, the lead Federal agency for Alzheimer's research. I'm accompanied by my colleagues today, Dr. Diane Murphy of the National Institute of Neurologic Disorders and Stroke; Dr. Judith Fradkin of the National Institute of Diabetes and Digestive and Kidney Diseases; and my NIA colleague, Dr. Marcelle Morrison-Bogorad.

With the rising number of older Americans, the prevention and treatment of these diseases has become an urgent public health priority, because these diseases disproportionately affect the older population. Nowhere is this more important than in the veteran population, where 37 percent are elderly, compared to 13 percent of the total U.S. population.

It is our hope that ournational investment in research will result in dramatic gains in our ability to understand, diagnose, treat, and ultimately prevent these devastating diseases.

Our efforts have been greatly enhanced through the involvement of veterans who participate in our research studies and the collaboration of many research scientists in VA.

Alzheimer's is a progressive neurodegenerative disorder that starts with mild memory loss but is relentlessly progressive until it destroys all cognitive function. About 4.5 million Americans, as you have heard, currently have AD at a cost of about $100 billion a year.

While National Institute of Health's Alzheimer's research program is quite broad, I'd like to highlight one area of our portfolio, the identification of those at highest risk for developing the disease, so that we can target early interventions.

In the past decade, we have identified three major gene mutations, as you also have heard, and I might add that one of these was identified by a VA investigator who was jointly funded by the NIH, and these genes were associated with the early onset form of the disease, and we have also found another gene, ApoE4, which is a major risk factor for the more common late onset form, and scientists have recently uncovered a set of genes that may influence not whether but when a person develops Alzheimer's.

In addition to age, epidemiologic studies have identified heart disease, high blood pressure, stroke, and Type 2 diabetes as risk factors for Alzheimer's, and through research using powerful imaging techniques such as positron emission tomography and magnetic resenance imaging or MRI's, we are opening new windows into the living brain as we move toward more sensitive and accurate tools for the early diagnosis of Alzheimer's.

I would like to also mention that we are currently supporting 25 Alzheimer's prevention and treatment trials, a number of which are conducted at VA medical centers, yet another way that our partnership has strengthened AD research.

I would like to turn now to Parkinson's disease, another debilitating neurologic disorder.

The loss of nerve cells that control movement and that produce the neurotransmitter dopamine leads to tremors, rigidity, and slowing of movement along with other symptoms. This affects about 500,000 Americans.

Many patients can be treated successfully with the drug L-dopa, but for some, the effect might not be long-lasting.

However, research has led to new opportunities for the improved treatment of Parkinson's patients. In the year 2000, the NIH developed a five-year plan, the Parkinson's disease research agenda, to capitalize on these emerging opportunities.

In mid–2002, in the second phase of this plan, a summit of outstanding scientists in the field was convened, and their meeting resulted in the development of a matrix which outlined short to long-range and low-risk to high-risk goals that address ways we can get around the road blocks to progress in Parkinson's research.

Clinical testing of promising treatments is a high priority at NIH.

As part of this effort, the NINDS has developed the neuro-protection exploratory trial, or NET-PD, which is expediting the selection and then testing compounds through use of a network of clinical sites around the country, and a collaboration of VA and NIH has led to the largest trial of surgical therapy to date, a study of deep brain stimulation with implanted electrodes.

Additionally, ongoing testing of gene therapy strategies and animal models of Parkinson's disease will guide us on the path toward new opportunities in human gene therapy.

The third condition I've been asked to discuss, diabetes, is an escalating public health problem in the U.S., sixth leading cause of death.

It lowers life expectancy up to 15 years and leads to kidney failure, lower limb amputations, blindness, and heart disease.

As you also have heard, 6 percent of the population, or some 18.2 million Americans, have diabetes. Ninety to 95 percent of those have Type 2, what was formerly known as adult onset diabetes, and nearly one-third of those with diabetes are unaware that they have the disease and therefore are not taking the steps proven effective in reducing its complications.

Prevention is the key to controlling the diabetes epidemic. The recently published results of the NIH's Diabetes Prevention Program showed that sedentary, overweight individuals at risk for diabetes including older individuals participating in the study could prevent or delay the disease onset through lifestyle interventions.

The NIDDK and the Centers for Disease Control are actively supporting translation of these important results into real health gains. They have recently launched the firstnational diabetes prevention program, Small Steps, Big Rewards. Its message is that, through moderate weight loss, 5 to 7 percent of body weight, 30 minutes of physical activity five days a week, and a healthy diet, diabetes can be prevented of delayed.

The NIH also coordinates the Diabetes Mellitus I inter-agency Coordinating Committee, which harmonizes diabetes activities across all Federal agencies. As an example of our collaboration, NIDDK and VA have jointly funded research on specialized footwear to prevent diabetic foot ulcers. Both agencies are also working together on thenational diabetes quality improvement alliance to improve adult diabetes care.

As our population rapidly ages, it is important that we continue to work with our Federal partners to find ways to effectively address these diseases that are associated with advanced age.

While we are making great strides, much work remains so that we can fulfill the promise of healthy old age for our veterans and for all Americans.

It is difficult to do justice in five minutes to all the exciting research that is occurring with Federal support, but I hope that I have conveyed to you some of the great excitement and hope with which we view our work.

I would be happy to take questions, as would my colleagues.

Thank you.

Prepared statement of Dr. Salerno appears on p. 33.]

Mr. BUYER. Dr. Salerno, will you please introduce the staff that you brought with you by their name and title, and please have them stand.

Dr. SALERNO. Dr. Diane Murphy from NINDS, who is our expert in Parkinson's disease; Dr. Judith Fradkin from NIDDK—who is our expert in diabetes; and Dr. Marcelle Morrison-Bogorad, who runs the NIA research program in Alzheimer's disease.

Mr. BUYER. All three are here and prepared to answer any questions that any of the subcommittee members may have?

Dr. SALERNO. Yes.

Mr. BUYER. Great. Thank you very much.

Dr. Kussman, those of us who control the ground and move the caissons, along with our comrades, the Marines, generals, I appreciate your opportunity to throw a bone to the lieutenant commander of the Navy. You have got to do that every once in a while.

So, sir, you are now recognized for five minutes.

STATEMENT OF MICHAEL J. KUSSMAN

Dr. KUSSMAN. Well, good morning, Sir. Good morning, Mr. Chairman and Members of the committee. I had no problem of your pulling rank, Sir.

I appreciate this opportunity to appear before you to discuss VA research into Alzheimer's disease, diabetes, and Parkinson's disease.

VA research is committed to better understanding the causes and developing treatments and preventive measures for these diseases.

With me today, besides the other distinguished witnesses here at the table, is Dr. Timothy J. O'Leary, Director of the VA's Biomedical Laboratory Research and Development Services.

Parkinson's disease is a slowly progressive disorder that results from the degeneration of nerve cells in a small area of the midbrain.

The prevalence of the disease, which afflicts over 500,000 Americans, increases with age. It affects 1 percent of the U.S. population over age 60 and 3.4 percent over age 74.

VA medical centers treat over 40,000 Parkinson's disease patients every year.

Over the past five years, VA funding for Parkinson's disease research has nearly doubled, with $10.1 million allocated for projects in fiscal year 2004. Since fiscal year 1999, non-VA funding has more than doubled.

Funded projects focus on various aspects of research, including the role of neurotransmitters, advances in neuro imaging technologies, gene therapy and animal models, mechanisms of damage to nerve cells, non-motor aspects of Parkinson's disease, rehabilitative strategies, and clinical trials of surgical treatment.

With the development of six Parkinson's Disease Research, Education, and Clinical Centers, or PADRECCs, VA took a major step toward improving patient care and outcomes while, over the longer term, pursuing a cure for Parkinson's disease.

Operating as anational consortium, the PADRECCs conduct research covering basic biomedicine, rehabilitation, health services delivery, and clinical trials.

They are also implementing a prospective patient care registry as a means of monitoring the care of veterans. The anticipated benefits are the improvement of clinical care by tracking the clinical status and interventions of veterans with Parkinson's disease.

Diabetes is a leading cause of disability and death in the United States. Complications include blindness, end stage renal disease, and amputation. Middle-age persons with diabetes have two to four

times the risk of coronary artery disease and stroke as do similar persons without diabetes.

Approximately 18 million people have diabetes mellitus, and each year, over one million more people over the age of 20 develop the disease.

Diabetes affects nearly 20 percent of veterans receiving care in the VA health care system, and veterans with diabetes account for nearly 25 percent of all pharmacy costs and for more than 1.7 million hospital days of care annually.

Over the past five years, VA funding for diabetes research has increased to over $16.8 million in fiscal year 2004. Since fiscal year 1999, non-VA funding has grown by more than $13 million.

Some of the areas of research include diabetes-related complications in aging and effects of exercise and diet, regulation of glucose transporters and gene transcription by insulin and glucose, pathogenesis and genetics of diabetic neuropathy and diabetic retinopathy, linkage analysis and genetic studies of type 2 diabetes, and rehabilitative strategies.

We have seen great improvements in the quality of care and health outcomes of veterans with diabetes as a result of the VA's Diabetes Mellitus Quality Enhancement Research Initiative.

This initiative will help identify and evaluate diabetes care practices, current gaps in care, and interventions to improve patient care outcomes.

It will facilitate the implementation of interventions and care processes that are most likely to produce substantial improvements in the quality and length of life for many veterans with diabetes.

Alzheimer's disease is a complex illness that causes the gradual loss of brain cells. It is the leading cause of dementia. Nearly 4.5 million Americans have this disease. It is a major cause of morbidity and mortality among veterans.

VA supports a broad array of studies on Alzheimer's disease. Over the past five years, VA funding for Alzheimer's disease research has increased to over $6.3 million in fiscal year 2004. Since fiscal year 1999, non-VA funding has increased by over $12 million.

Some of the areas of research include vaccine development, advances in neuroimaging technologies, gene therapy in animal models, mechanisms of damage to nerve cells, inflammatory mechanisms, gene-environment interactions, and therapeutic interventions.

VA has recently funded several significant studies on the quality of care and outcomes of veterans with Alzheimer's disease.

Investigators have demonstrated that veterans with dementia who receive appropriate interventions from care givers might be able to remain at home longer in environments that promote maximum independence for both caregivers and patients.

Researchers have also revealed a significant relationship between discomfort and agitation among nursing home residents with dementia, suggesting that agitated behaviors may be associated with increased pain. Accordingly, better quality of life for long-term care residents may result from regularly scheduled pain management.

We are very proud of the VA's accomplishments in Parkinson's disease, diabetes, and Alzheimer's disease research, and we remain

committed to maintaining the highest quality research in the country to best serve the needs of our Nation's veterans.

Mr. Chairman, this concludes my opening statement. My formal statement has been submitted for the record.

Dr. O'Leary and I will now be happy to answer any questions that you might and other members of the subcommittee might have.

Thank you.

Prepared statement of Dr. Kussman appears on p. 46.]

Mr. BUYER. Thank you, Dr. Kussman.

I now recognize Dr. Franklin Zieve, the Associate Chief of Staff for Research, Richmond VA Medical Center.

STATEMENT OF FRANKLIN ZIEVE

Dr. ZIEVE. Thank you, Mr. Chairman.

I speak to you today in a dual role. For 27 years, I have been associate chief of staff for research at Richmond, and I also am director of our diabetes health center. I am going to confine my remarks strictly to what is going on in Richmond, but I think virtually every VA medical center would have a comparable story.

I am not going to tell you that diabetes is getting more common, because you have already heard that three times, but I can give you a quick reason as to why: a year from now, all of us will be one year older and, on the average, will weigh a pound-and-a-half more than we do today, and a larger fraction of us will have diabetes.

Well over half of the heart attacks in this country occur in people who have either diabetes or its precursor, which is variously known as pre-diabetes or the metabolic syndrome, and most heart attacks, like all other complications of diabetes, are preventable. The problem with Type 2 diabetes is that there are so many of them that technically doing the prevention becomes very difficult. Any of us could give great care to 50 diabetics, but we have 6,000 of them in Richmond alone.

The main reason I am still in the VA after 33 years of Federal service is that I feel that VA is a uniquely favorable place for giving good diabetes care. One of our advantages you mentioned, Mr. Chairman, in your initial statement, our computerized patient record, which is just a tremendous advantage which enables us to see when we are doing things poorly, and the biggest advantage we have is the veterans themselves, who I think are uniquely rewarding and good patient population to work with.

I would like to address how research fits into our clinical operation. The VA research program covers a wide spectrum of studies ranging from cloning genes to how you structure the delivery of care, but all of these have in common that they are patient-focused.

The most basic VA projects grow out of what we see clinically every day. For example, the fundamental driver of the increased prevalence of diabetes is our society's epidemic of obesity, and my colleague, Dr. Jim Levy, runs our weight management program and finds, as does every weight management program, that getting people to lose weight is easy. The problem is they regain it promptly, and this led him to study the regulation of leptin, which is the hormone from adipose tissue which regulates both appetite and en-

ergy expenditure, and his studies in rodents have produced some unexpected findings.

For example, he found when rats were fed omega-3 fatty acids in the form of fish oil, they tremendously increased their energy expenditure. I do not know how many of us would have thought of feeding fish oil to rats—rats, incidentally, love fish oil; they just lap it up—but the idea came from some patients with the metabolic syndrome who we treated with fish oil for their high plasma triglycerides and unexpectedly found that their fatty livers went away.

So this is an example of basic research flowing directly from clinical care.

Dr. Kussman mentioned the VA diabetes trial in which we are a site, and I will not talk about it further other than to point that however this turns out, it is going to establish an international standard of care on a rather important issue.

I will talk briefly about our research that addresses therapies that we know work but that are hard to apply in clinical practice. For example, I mentioned that well over half the heart attacks in this country happen to people who have either the metabolic syndrome or diabetes.

Most of these could be prevented if everything that we know works were implemented maximally—lifestyle changes, cholesterol and triglyceride lowering, blood pressure control, aspirin, beta blockers, ACE inhibitors, you name it. The problem is how to apply these effective therapies to the large numbers of patients who would benefit from them.

So our current health care delivery research at Richmond involves a pilot metabolic syndrome clinic in which a group of these veterans who have such high heart attack risk has six monthly visits in which we gang tackle their cardiac risk factors.

Five hundred veterans have completed the full sequence as of last week.

One of our patients referred to this program as boot camp, but all of us have been very impressed with its effectiveness. Over 70 percent of the patients have achieved their very stringent lipid and blood pressure goals.

Everything we do in this clinic has long been known to reduce coronary risk, but in the country as a whole, most people at high risk do not fully benefit from these therapies, because it is hard to apply them to the numbers involved.

This is an example of how VA can function as a laboratory for finding the best ways of taking therapies which we know work and applying them in real life.

Mr. Chairman, I have tried to give a few examples of the spectrum of diabetes research in Richmond and to show how it all flows directly from VA medical care, which is our primary focus, and I will be happy to answer any questions.

Prepared statement of Dr. Zieve appears on p. 55.]

Mr. BUYER. Thank you.

I now recognize Dr. Robert Ferrante, the Director of Experimental Neuropathological Program, Geriatric Research, Education, Clinical Center, Bedford VA Medical Center.

STATEMENT OF ROBERT J. FERRANTE

Dr. FERRANTE. Thank you, Mr. Chairman, members of the subcommittee. I am pleased to appear before the committee to discuss Parkinson's disease research within the VA and as it pertains to the Bedford VA Medical Center.

The broad goals of the VA health care system remain constant in the mission to treat, cure, and if possible, to prevent disease while providing the best possible health care to veterans. As part of this mission, the VA has developed a well regarded medical and scientific research program.

Brain diseases have a devastating impact upon veterans. As the veteran population ages, the incidence of these neurological conditions will substantially increase. The VA has made a serious commitment to improving patient care and identifying a cure for brain diseases, particularly Parkinson's disease.

Parkinson's disease, or PD, as it is called, is the second most common neurodegenerative disorder, affecting more than half a million Americans. It is projected to surpass cancer as the second most common cause of death among the elderly by the year 2040.

PD results in a loss of specific neurons in the midbrain, causing tremors, slow movement, stiffness, and gait problems. The disease is highly debilitating, interfering with employment and normal activities of daily living.

There are approximately 50,000 new cases diagnosed each year. The VA medical centers treat at least 40,000 PD patients each year, and despite the many advances in therapy, no drug treatment appears to slow or prevent disease progression.

While the specific cause of PD is unknown, a number of hypothetical causes have been suggested, with evidence for a role of both environmental and genetic causes. Studies have suggested that PD is associated with exposure to pesticides and industrial chemicals. Other investigations have clearly identified genetic mutations that contribute to PD.

The VA has played a significant role in the current understanding of Parkinson's disease, as evidenced by the large public action record of VA clinical and scientific investigators. The VA research has helped to describe the fundamental clinical, pathological, and molecular features of Parkinson's disease and related disorders.

The VA is now at the forefront of developing a therapy for PD. In 1999, the VA and the National Parkinson's Disease Foundation established an alliance dedicated to finding a cure for the disease, confirming the VA's commitment to understanding Parkinson's disease.

In 2001, as Dr. Kussman reported, the VA announced an innovative health care delivery model for veterans with Parkinson's disease by opening six new Parkinson's disease research, education, and clinical centers, PADRCC's, as they are called, specializing in Parkinson's disease research, education, and clinical care.

Each PADRCC is involved in basic bio-medical research, rehabilitation, health services delivery, and specialized clinical trials.

In 2003, the VA developed anational consortium network for dispersed VA clinicians to resource the VA's expertise in PD through

the PADRCC's. The consortium is now comprised of 150 multi-disciplinary clinicians.

I direct a research program at the Bedford VA developing therapies for neurodegenerative disorders that are particularly focused upon finding a treatment for Parkinson's disease, Lou Gehrig's disease, and Huntington's disease. We use scientific models of Parkinson's disease to test the effects of drug compounds to prevent the cell loss that may result in the clinical and pathological picture of Parkinson's disease.

Once these drugs are found to work in neurological models, human clinical trials are begun through the VA clinical trials program.

We now have a number of very promising drug therapies to slow the progress of PD and other like brain disorders such as Lou Gehrig's disease.

The VA is an excellent and productive training ground for future investigators in Parkinson's disease. The influence of the VA extends well beyond its boundaries. The success of the VA research program in PD is based upon strong institutional commitments by the medical service and a cohesive community of scientists and clinical investigators.

The VA will build upon these past accomplishments and will continue to conduct research that will ultimately help in the search for a cure for Parkinson's disease. The VA is positioned and ready to meet this challenge.

That concludes my statement, and I would be pleased to answer any of your questions.

Thank you very much.

Prepared statement of Dr. Ferrante appears on p. 58.]

Mr. BUYER. Thank you.

We now recognize Dr. Mary Sano, associate chief of staff of research, the Bronx VA Medical Center.

STATEMENT OF MARY SANO

Dr. SANO. Thank you, Mr. Chairman and members of the subcommittee.

Though new to the VA, I have been a researcher in Alzheimer's disease for nearly 20 years, with a primary interest in developing strategies for the treatment and prevention of the disease.

Currently, I am a director of a multi-center clinical trial to determine if lipid-lowering drugs can slow the progression of Alzheimer's disease. This is run with a consortium of Alzheimer's centers around the country and includes several other VA sites.

The Alzheimer's Disease Research Center, located at the Bronx VA Medical Center and the Mt. Sinai School of Medicine in New York City, which I direct, provides an infrastructure to use state-of-the-art clinical assessments of patients and to offer patients the opportunity to participate in cutting edge research.

One of the most valuable resources at our medical center is the brain bank for Alzheimer's disease and other cognitive disorders. This resource permits us to conduct clinical neuropathological correlations to determine the changes that occur in the brain with aging and disease.

Because of the careful clinical diagnosis and electronic record-keeping of the VA medical centers, we are able to maximize the very generous contribution of the volunteer veterans to compare detailed information from their medical records with subtle and microscopic changes at the cellular level and to get a clearer picture of the biology of Alzheimer's disease.

For example, the area of the brain known as the entorhinal cortex and the hippocampus appear to deteriorate very early. These brain areas are involved in memory and learning, and we now know that serious impairments in memory may predict AD several years before the disease can be diagnosed.

VA has a long history of research in Alzheimer's disease. The very first multi-center study for an approved treatment for Alzheimer's was published in the New England Journal under the leadership of a VA physician, the former chief of psychiatry at the Bronx VA. This work made a longstanding contribution in that it provided the methodology for conducting multi-center studies for testing new treatments for Alzheimer's disease. That methodology is still used effectively today.

In particular, the very test used to determine drug efficacy in dementia in nearly all pivotal studies is the Alzheimer's disease assessment scale, which was developed at the Bronx VA. Though this test was published nearly two decades ago, it remains the most commonly used assessment in clinical trials for Alzheimer's disease in the United States and around the world.

Many renowned VA AD research colleagues who have been in the field for many years have made important contributions from bench to bedside.

This is the challenge for VA research, and it is met, for example, through pioneering work examining fiber-blasts and other cell types which have led to the first clinical trials in gene therapy for patients with Alzheimer's disease.

While finding cures and prevention are important, even our best efforts will leave many patients with this disease. VA researchers have done cutting edge work to define and maximize patient independence and comfort. This rigorous research lays the foundation for determining the best way to evaluate a patient's ability to participate in clinical and research decisions.

In summary, the success of AD research in the VA is a result of a series of partnerships.

These partnerships begin with the generous spirit of the veterans who volunteer to participate. They include the melding of clinical resources such as the electronic medical records system and centralized databases, with the outstanding curiosity of the VA researchers, and it would not be possible without the research resources to make the best use of these scientific opportunities and the commitment to deliver the best of care.

Thank you for allowing me to make this statement. I will be glad to answer questions.

Prepared statement of Dr. Sano appears on p. 61.]

Mr. BUYER. Dr. Kussman, I was taking note of the Office of Research and Development's budget from fiscal year 1999 through fiscal 2003. The numbers that I have show the budget increased on research from 300—these are appropriated dollars—from 300—I

am using approximate—309 million in 1999, increased to 392 million in 2003. I do not have the 2004–2005 with me, but there has been an acceleration in the budget.

Would you please tell us about what the total—what is the total research dollars to the VA, not just our appropriated, but when you include the private companies and foundations, and if you know what they are for the top subject areas.

Dr. KUSSMAN. Yes, sir. The total is about 1.1 billion.

Mr. BUYER. About $1.1 billion?

Dr. KUSSMAN. Yes, sir.

Mr. BUYER. Would you have a breakout?

Dr. KUSSMAN. The $392 million that you mentioned are the appropriate dollars. The other $700 million is about half and half between——

Mr. BUYER. When you take the $1.1, the $1.2 billion and put that into areas of research, would you have a breakout of how you are spending the money?

Dr. KUSSMAN. We can get you that, sir.

Mr. BUYER. I will tell you what. I will give your staff about 10 minutes to figure that out. We will come back and ask that question.

Dr. KUSSMAN. I have the list here of the top 10 conditions that we are doing.

Mr. BUYER. There you go. Please.

Dr. KUSSMAN. In mental health, the total number is $220 million; cancer, $157.3 million; heart disease, $81.9 million; aging, $71.2 million; substance abuse, $59.4 million; AIDS, $54 million; Alzheimer's, $51.5 million; neurodegenerative disease, $51.2 million; diabetes, $48.8 million; and prostate disease, $41.3 million.

Those are the top 10 conditions.

Mr. BUYER. Of diabetes, do you know what the approximate cost is to the VA with regard to treatment of diabetes? About how much percent of your health budget is diabetes-related?

Dr. KUSSMAN. I believe, as I mentioned to you, that about 20 percent of the patients have diabetes, and I believe about 27 percent of the budget is spent on diabetes. 6.8 percent of the medical care dollars go to the care in diabetes.

Mr. BUYER. Wait a minute. Time out. I did not make this number up, but I read somewhere that somebody wrote that approximately 25 percent of the VA cost is diabetes-related with regard to health care? Is that accurate?

Dr. KUSSMAN. Yes, sir. The total amount of dollars, because there is multi-factorial of the patients with diabetes have heart disease and other—hypertension and other things, and so, the total amount of the budget, as I understand it related to the full spectrum of patients with diabetes and other related costs, comes to about the 25 percent of the total budget.

Mr. BUYER. Would it be fair to say sometimes it is hard to determine.

Dr. KUSSMAN. Yes, sir.

Mr. BUYER (continuing). Doctors use testimony that half of all heart attacks are some form of diabetes-related or precursors, and so, it is relatively hard to say the exact number.

Dr. Salerno, I recall testimony on the subcommittee of the commerce committee that about one-third of your Medicare expenditures is diabetes-related. Is that still accurate?

Dr. SALERNO. I am not certain about that.

Dr. FRADKIN. I am Judy Fradkin from the National Institute of Diabetes and Digestive and Kidney Diseases. The answer depends on whether you consider all health care costs of people with diabetes or costs that are directly related to care of diabetes itself. You also have to consider that illnesses that a patient with diabetes develops cost more to treat.

For example, if a patient with diabetes has a heart attack or has pneumonia, they spend longer in the hospital and the cost of taking care of the pneumonia and the heart attack is greater for a person with diabetes than if the same condition occurred in a patient without diabetes. So, when we consider the costs, we are considering both the costs of diabetes and the added cost of conditions that occur in patients with diabetes that could be attributed to the diabetes.

Mr. BUYER. Often here we look at how we leverage dollars, and I note that simple math here, Dr. Kussman, is that your diabetes research is 4.6 percent of the whole. So, what we have here are very limited dollars going to research in diabetes where, in fact, we are spending a lot of money on the back end.

I just want to let you know we note that.

I also understand that you have a three-minute video that shows some very impressive results with regard to deep brain stimulation with regard to the VA's Parkinson's research.

Would you please share with us your video?

Mr. KAPLAN. Roger Kaplan, special assistant chief research and development officer.

This is footage of a participant prior to his DBS surgery, Mr. Chairman, and he is walking to a pre-selected spot which will also be seen in the following video. He has been off of medications for approximately 12 hours.

Dr. FERRANTE. Deep brain stimulation involves exciting certain parts of the motor pathway in patients, so that there is constant stimulation as dopamine would normally do.

Dopamine, the neurochemical that helps in movement transmission, is lost in Parkinson's disease patients, and this helps actually as a symptomatic treatment.

It is not a curative treatment but a symptomatic treatment, helping patients in regard to their movement disability.

Typically, an electrode is placed in parts of the different connections over the motor system that is within the brain and constantly stimulates or activates that particular system, so it equilibrates the system, as if it would if there were normal dopamine levels.

There is a second part to this apparatus. The apparatus is controlled by an element that is placed in the chest in order to continually stimulate the brain.

That particular piece can be changed after a number of years, two to four years, depending upon the life of the system, and there are, in some instances, in very small instances, where relocation of the electrode needs to be placed and reoriented within the brain.

Mr. KAPLAN. Mr. Chairman, the last video took approximately two minutes, 48 seconds for the veteran to stand, walk, turn around, return to his chair and sit down. We will now show you footage of the same veteran following his DBS surgery.

[Videotape is played.]

Mr. BUYER. That is remarkable.

Mr. KAPLAN. Approximately 20 seconds, Mr. Chairman.

Mr. BUYER. How long does this surgery take, the procedure?

I mean tell us a little bit about how long—how difficult—and the cost.

Dr. FERRANTE. Usually, deep brain stimulation, in the past, was used primarily when other pharmacologic treatments were no longer working.

Typically, some of the symptomatic treatments using L-dopa and combinations of L-dopa had difficulty in their clinical use after five to six years, and deep brain stimulation was used primarily for patients having difficulty with symptomatic drug treatment.

We now understand or have an understanding that DBS may be used well in symptomatic treatment in many PD patients.

Surgical treatment is relatively expensive. It costs $20,000 per patient.

The implantation requires in-patient neurosurgery. Again, there is an electrode that is placed from the top of the skull and placed within certain parts or a single part of the motor system that helps to control it. In some events, two electrodes are placed in the brain—one in both sides, so that there is bilateral implantation of electrodes, and the system is operated via a connection from under the skin and back into the chest.

Mr. BUYER. Who has the patent on this? Was this done based on VA research dollars, and if so, was there a cooperative technology administration agreement with the founders?

Dr. KUSSMAN. Mr. Chairman, I'm not sure I can answer the question about who has a patent, but right now, it is approved by the FDA.

We have a cooperative study going on now, and our patients basically have the option of participating in the study or getting the deep brain stimulation off study, because it has been approved by the FDA as an acceptable therapy.

My understanding of the study is that it is one of the largest studies going on in the country to look at more than one site of the stimulation in the brain and compare it to the medical therapy.

We are about halfway through that cooperative study, and we hope to have some exciting results from that.

Mr. BUYER. If I could ask for tolerance from my colleagues for just a follow-up question, what I am trying to ask here is, for a long time, the VA and NIH, both, but particularly the VA, we have invested a lot of money, and we are trying to seek our patent rights from the government, because we invest the taxpayers' dollars and these universities and others then reap benefits, and from the VA, we want those benefits to come back to the VA.

So, I was just curious, and if you do not have the answer today, if you could get us for the record whether or not any VA research dollars were part of this, and if so, was there a cooperative agreement with regard to patents.

I now yield to Ms. Hooley for any questions she may have.

Dr. KUSSMAN. We will have to get back to you.

(See p. 89.)

Mr. BUYER. Okay. Thank you.

Ms. HOOLEY. Thank you, Mr. Chair.

The subcommittee selected those three disease that are prevalent in the aging population.

Dr. Salerno, what other diseases are out there that you think will be a serious threat to the aging population in the future?

Dr. SALERNO. The diseases that affect the main causes of death and disability in the country—cancer, heart disease, stroke—are also, diseases of aging, and the costs associated with it are because people are also living longer with these diseases as we have been able to increase survival.

Ms. HOOLEY. What disease do you think will be the most costly in the future?

Dr. SALERNO. Well, it is hard to speculate, because it really depends on how well we do with finding effective interventions.

For instance, the cost of caring for an Alzheimer's patient for one year is over $30,000, and as the population ages, unless we find effective interventions, it will be at a cost of hundreds of billions of dollars to the health care system.

Ms. HOOLEY. In your testimony, you talked about the sharp increase in the number of patients with Alzheimer's and that it is increasing and there will be a threefold increase by 2050. Do you foresee some kind of—a cure or help or preventative measures that can happen in the next 40 years?

Dr. SALERNO. Well, I began in Alzheimer's research in the late 1980s, and the words "prevention" and even "treatment" were not in our vocabulary then. I think that the pace of the science in the last 15 years has been remarkable.

We now understand more about the disease, about the basic biology of the disease. We are now understanding—getting closer to being able to make a more definitive diagnosis in living human beings.

We have remarkable technology that helps us image the living brain, and all of these things, I think, have really pointed us in a direction where we are very optimistic that, while we cannot predict when we see cures or more effective treatments but that we are certainly headed in the right direction, and I think that this is a testimony to the payoff from the great Federal investment in research in this area.

Ms. HOOLEY. To any members of the panel, is there anything—we talked about—in diabetes, we talked a lot about what we can do to prevent diabetes. I mean it is lifestyle, it is weight, it is exercise, those sorts of things.

What can the average person do to help prevent Alzheimer's and Parkinson's? If I went out and said, you know, if you do this, it will help delay it, it will not come on as fast, what are those preventative measures a person could do?

Dr. SANO. Because we have a disease that occurs so late in life, it is difficult to answer these questions. However, we do have epidemiology studies that have suggested to us that many of the things that keep one's heart healthy also may keep their brain

healthy. There is evidence that control of weight and lipids may be important. There is evidence that keeping oneself active is also important, both cognitively active and physically active.

These are not guarantees, but there seems to be a strong connection between taking care of your general health and keeping your cognition high for as long as possible.

Ms. HOOLEY. Anybody else?

I have one other question. Actually, I have a whole bunch of other questions, but when you look at research dollars from VA, NIH, do you look at putting more money into those areas that are the most costly? I mean when we talk about how much it costs to treat a person, for example, with diabetes and all the other related problems, or how much it costs to treat somebody with Alzheimer's, do we ever match the research dollars with those diseases that are—affect more people and that cost more? I mean is that ever done?

Any one of you.

Dr. SALERNO. At the NIH, each individual institute is given a separate appropriation by Congress, but within that, we all develop strategies for our investment to maximize—for instance, in the National Institute on Aging, about 50 percent of our budget, about half a billion dollars, goes to Alzheimer's research, because it is one of the most pressing public health issues that we are facing.

Ms. HOOLEY. So within the aging budget, 50 percent.

Dr. SALERNO. Yes.

Ms. HOOLEY. What percent of the budget is for aging for NIH?

Dr. SALERNO. Well, again, it is difficult to tease that out specifically.

We have some idea by diseases. For instance, all of Alzheimer's research is about $650 million across the NIH, but there are diseases of aging that affect almost every organ system, and so, we try to leverage, just the way there is leverage with the VA research dollars, we try to leverage our investment so that, for example, we invest in putting an aging focus in comprehensive cancer centers to—to cut across all of the areas that are important.

Dr. O'LEARY. This is Dr. O'Leary. From the VA perspective, we are actually currently reviewing the portfolio allocations to better understand the relationships, but it is a combination of things that goes into decisions.

Certainly, much of our research is driven by the patient population that we see, because that is reflected by the clinician population that develops good ideas that should be funded.

In addition, though, there are areas that are sometimes targets of opportunity, which seem to be a little bit more ripe for research investment. The presence of targets of opportunity also has an influence on the way research dollars are invested. Finally, as mentioned just a moment ago, the leveraging opportunities not only with other groups that can fund, but also opportunities within a particular research project. In many cases research, particularly our basic research is not really just devoted to a single disease but, in fact, can have implications for treatment of a number of different diseases and conditions, and so, the portfolio is kind of hard to match one-to-one with a disease.

Ms. HOOLEY. I know there is probably not a one-to-one match, but what are—I mean as you are looking at the diseases, the opportunities in that relationship, what do you see on the horizon?

Dr. O'LEARY. Well, there are a variety of things.

First of all, we have military-unique things to consider, things that are affecting our veterans as they come immediately off active duty, particularly now, and this is getting into an area of very high attention and priority. Certainly, areas like diabetes, mental health, and the neurodegenerative diseases have all been areas in which there are targets of opportunity. Infectious diseases have been targets of opportunity.

The delivery of health services, the way to most effectively use our resources in order to get veterans the care they need is also part of our research focus. Finally, there is a very special emphasis in VA on rehabilitation research and particularly things that have to do with spinal cord injury, which has been one of the great success stories of VA research.

Ms. HOOLEY. Thank you.

Mr. BUYER. Mr. Evans, you are recognized?

Mr. EVANS. Thank you, Mr. Chairman.

On this issue of the deep brain stimulation, why isn't it more prevalent? I think it has not been utilized particularly, and if that is true, what, if any, of the effects would be helped by deep brain stimulation?

Since every Parkinson's disease patient has different symptoms, how do we determine what is a success? Is it elimination of all those different symptoms?

Dr. FERRANTE. There are a number of treatment therapies, and those that currently work best are the symptomatic therapies. Deep brain stimulation is considered to be a symptomatic therapy.

As with any of the pharmacological treatments, a patient needs to be closely monitored and watched, and that equally occurs with deep brain stimulation in regard to the constant pulsing of certain parts of the brain.

It is thought that dopamine constantly pulses the motor system to keep it in balance, and it is the use of this particular technique, deep brain stimulation, that provides symptomatic relief.

You are absolutely correct, sir, that each patient is, in large degree, going to be treated individually, and it is important that there be continued assessment of the progress in regards to their motor abilities with this particular symptomatic treatment.

Dr. KUSSMAN. Sir, maybe I could add just a little bit to that response, if I might.

We have a quality indicators project going on, looking at what the quality indicators would be for outcomes related to patients with Parkinson's disease, and these have been established by subject matter experts, and so, we can try to assess the different therapies with the different symptom complexes, looking at these quality indicators, and then follow the patient appropriately.

So that's one of our projects.

Mr. EVANS. From my understanding, the VA is not giving the stimulation at this point for veterans, or is that not a problem? What is the eligibility of a veteran for getting these treatments?

In other words, what I am asking is who is going to determine who gets the expensive treatment? We have 40,000 veterans, as one of you had testified. If we had that many, how much would that cost, or is the VA actually not doing the deep brain stimulation? Are they just doing research at this point?

Dr. KUSSMAN. No, sir. We are doing it—as I mentioned earlier, I think—two processes—one is the research project, but we are also doing it for patients on a routine basis, if you can ever say it is routine, because it is an accepted, approved FDA modality of therapy for Parkinson's disease.

So you do not have to be part of the research project if you don't want to.

Mr. EVANS. Okay. All right.

Thank you, Mr. Chairman.

Mr. BUYER. Mr. Boozman, do you have any questions?

Dr. Salerno, on page 2 of your testimony, you state that "Partnerships with VA researchers have strengthened our search for ways to delay and ultimately to prevent the devastation of Alzheimer's."

Could you elaborate on the partnerships that are involved?

Dr. SALERNO. Certainly.

The 29 Alzheimer's disease centers from across the country have multiple interactions with VA sites, and in fact, there is an overlap with places like Bedford and the Bronx.

Dr. Sano is a VA researcher, and she is also funded by National Institute on Aging in her Alzheimer's work, and she is part of the Alzheimer's disease center consortium group for research.

So there is considerable overlap, and in the centers where there is co-located GRECC, as well, there is a lot of opportunity for interactions, and it is a seamless interaction, since I have been on the VA side and the NIH side, and I can attest to that, and there are a number of GRECC researchers, too, the Geriatric Research Education Clinic Centers, who are perhaps not involved in the ADC centers but are also funded, and again, the—I think it has been very fruitful in terms of leveraging the opportunities and the resources and maximizing the investment from both sides.

Mr. BUYER. Dr. Sano, what would be your views on the collaborative effort?

Dr. SANO. Well, the collaboration really permits a wide range of benefits. The opportunity for the VA physicians to work closely with the researchers in the local affiliate is a strong method for strengthening the research environment. It is also an advantage to the patient population, since together they can get the most opportunities to participate in the cutting edge of the most recent research.

Mr. BUYER. Dr. Salerno, what are the top 10 funding priorities in research at NIH? Do you know?

Dr. SALERNO. For the entire NIH?

I can probably—I cannot speak for all the other institutes, but I can speak to one major priority, and that is our director Dr. Zerhouni's road map, and that is where we are looking at issues and opportunities which cannot be accomplished by one institute alone, that we need to invest in new scientific pathways, re-engineering the clinical research enterprise, and developing the re-

search teams of the future so that we will be poised to take advantage of those opportunities, and those are really cross-cutting, and the grant funds available from our road map activities are available for all researchers across all disciplines and all areas of interest.

So that is really, I think, what we are doing to really make sure that we can rapidly not only find discoveries—make these discoveries but disseminate them so that they translate into real health gains for the U.S. population.

Mr. BUYER. Ma'am, if you could, for the record, let us know what are the top 10 funding priorities in research at NIH, I would appreciate that.

I also recognize in the director's comments that he made about his road map that fingers without a palm does not make a hand—I thought that was a pretty good analogy, and just as here in the VA we are trying to eliminate these stove pipes and have greater interaction and operabilities and the sharing of information between different agencies—you have how many, 17? No, you have 27?

Dr. SALERNO. Twenty-seven different institutes and centers.

Mr. BUYER. You all cannot talk to each other. It just blows my mind.

Dr. SALERNO. We are trying.

Mr. BUYER. I know. You are getting there. We want to help you in that endeavor.

On page 11 of your testimony, you talked about a new program called MOVE, an acronym for Managing Overweight and Obesity Among Veterans Everywhere, which was developed by the VA National Prevention Center with assistance from NIH scientists and is being piloted at 17 facilities.

How long will this pilot last, and how many individuals will be involved?

Dr. SALERNO. Could I ask Dr. Fradkin to respond to that?

Mr. BUYER. Yes.

Dr. SALERNO. She's been involved in that effort.

Dr. FRADKIN. We just heard a presentation about this at our Diabetes Mellitus Interagency Coordinating Committee. This is a Congressionally established committee that is now in its 30th year which addresses this whole stove piping issue that you were just talking about. It brings together 23 different components of the government to work together on diabetes.

The MOVE program was developed with assistance from NIDDK scientists who have been directly involved with the obesity research effort and are very familiar with best practices that have been developed with NIH resources. They then worked with VA scientists to develop a program that could be implemented in the VA.

I believe that it is being piloted now at the VA, and then based on the results of those pilots, the VA will make a decision as to future deployment of resources. I think the VA, rather than the NIH, would be best able to speak to what the VA's plans are for that program.

Mr. BUYER What tools are you using for measurable outcomes?

Dr. KUSSMAN. Yes, sir.

The MOVE project has been led by the VA center in Durham for the prevention and—it is being piloted. It is a very aggressive program, and we are very excited about helping people in the whole spectrum of exercise and wellness and the purposes related to weight issues in the whole spectrum of diseases.

There are a set of criteria—and we will be happy to give you a official report on that that looks at the program and sets up the performance standards and things that we will be happy to report back to you.

(See p. 89.)

Mr. BUYER. Thank you.

Ms. Hooley, you are now recognized.

Ms. HOOLEY. Thank you, Mr. Chair.

Anyone on the panel, does it make any difference if you have early diagnosis of Parkinson's or Alzheimer's, and what tests do you use to diagnose people early for those two diseases?

Dr. SALERNO. Well, I can speak to the Alzheimer's early diagnosis.

That is a key element of our research strategy right now, because we believe that the changes occur in the brain at least a decade before there is any clinical symptoms and that since it is a disease of aging that even delaying the onset of symptoms by five years would have a remarkable impact on the incidence of the disease and also the quality of good cognitive life.

So we do not have a definitive way to diagnose at this point, but we have a multi-prong effort for research to help us develop the early diagnostic tools.

Ms. HOOLEY. So if you diagnose them early and you say you can, you know, delay the onset for five years, how do you delay the onset? What do you do with that early diagnosis?

Dr. SALERNO. Well, that is our hope, that some of the interventions, some of which look promising and are in clinical trials now in early Alzheimer's patients, that if we can put them into—if we can use them before there are any symptoms, that since we know these diseases slow the progression, it may slow them enough for a long enough period of time so that you will be in a clinically disease-free state for longer periods of time.

Ms. HOOLEY. One of the tests I want to ask about—research have recently developed the first radio-tracers, including a molecule called Pittsburgh compound B, that facilitate visualization of depositions in living AD patients using PET scans. Do you use that? Is that procedure used in the VA?

Dr. SALERNO. This is a very new research finding, just came out within the past few months——

Ms. HOOLEY. Okay.

Dr. SALERNO (continuing). And it needs to be confirmed and we need far more data, but it is the first time that there are clues that we can visualize the pathologic changes in the brain of an Alzheimer's—of a person early in the disease. So, this is—these kinds of things are where we hope to see the payoff so that we can really define the diagnostic techniques that will lead to the early interventions.

Ms. HOOLEY. Has this been used at the VA?

Dr. KUSSMAN. Not that I am aware of, because it is considered a research project right now, and as it evolves and if it turns out to be something that would be appropriate therapy, obviously we would use it as we do all other types of appropriate therapy.

Ms. HOOLEY. What do you use to diagnose Alzheimer's right now? I mean if you talk about early detection—I mean why would a person go and say, gee, you know, I need to be tested? Is it because you have parents, family members? Is it hereditary? Why would I go and get an early diagnosis for Alzheimer's or Parkinson's, I mean either one of those?

Dr. SANO. In the case of Alzheimer's disease, one of the earliest detections is memory impairment, and it is particularly when memory problems are noted by someone in the family of the patient, by a loved one, who notices a change.

The value of doing that early is that one can make the most use of the current treatments, but it is also to ensure the safest environment that they can live in while they have even these early symptoms and can allow them the maximum freedom if they know limitations very early on.

Ms. HOOLEY. What do you use to diagnose it?

Dr. SANO. The diagnosis is based on documenting the memory impairment, the functional loss, and the potential behavioral problems and ruling out any other medical conditions that might contribute to those kind of problems.

Ms. HOOLEY. What do you use to diagnose Parkinson's, and is it important to also get to that early?

Dr. FERRANTE. Well, again, it is a clinical diagnosis, and as with many of the neurodegenerative disorders and neurologic diseases, there is some specificity in that regard.

There is an issue with Parkinson's disease. There is a phenomenon referred to as Parkinsonism, that results in Parkinson's disease-like conditions, and so it is important, as Dr. Sano has indicated, to clearly differentiate which is idiopathic Parkinsonism, which we are talking about here today, versus other disorders.

I think one of the very important partnerships that have recently developed between NIH and the VA is the translational program, identifying bio-markers and a variety experimental models to characterize those bio-markers, as well as to identify selective neuroprotective therapies.

Ms. HOOLEY. Is it important to have an early diagnosis? Does it make a difference if you have an early diagnosis of Parkinson's or not?

Dr. FERRANTE. Yes, it does in regard to the patient's clinical care. However, one of the issues is that we still do not know the causal event of Parkinson's disease.

Ms. HOOLEY. So we cannot postpone that if we know it early.

Dr. FERRANTE. Yes, we can. We can slow the desease process with neuro-protective drug compounds, and as I was saying, the partnership between VA and NIH is currently identifying drug treatments that will slow or prevent continued neuron loss in the brain.

Ms. HOOLEY. Okay. Thank you.

Mr. BUYER. Mr. Evans, you are now recognized.

Mr. EVANS. Thank you, Mr. Chairman.

Do we know how many veterans have been given the brain stimulus treatment in the VA in the last year or so?

Dr. KUSSMAN. A hundred and thirty-eight.

Mr. EVANS. Okay.

Thank you, Mr. Chairman.

Mr. BUYER. Mr. Boozman?

Mr. BOOZMAN. Yes.

Mr. Zieve, in your presentation, you talk about the problems related to diabetes in relation to heart disease, and yet, you know, when we hear others testify in other settings, the main concern seems to be with blindness and kidney failure.

Is there a reason that you have kind of hit the heart disease harder?

Dr. ZIEVE. In people who present with diabetes at an early age, blindness and kidney failure, the microvascular complications, are the biggest problem they run into, and these are preventable.

In the adult age group, the VA age group, and the majority of people with new diabetes today, they are not going to go blind from their diabetes, because they are going to die of a coronary first.

We actually wish that we had more of a problem with preserving vision, but we have to get by this tremendous vascular incidence first, and I think probably what has happened is, number one, diabetes is being a little better controlled so the people are living longer, and number two, because of the increased prevalence of obesity in our society, the diabetic is a little heavier, he is a little more insulin resistant, he is going to be at a little more heart attack risk. Coronary disease is the big blight on Type 2 diabetics today, and this is going to become an increasing problem at younger ages, because the obese teenagers who are presenting with diabetes at age 15 are going to present with their coronaries at age 35 or 40.

Mr. BOOZMAN. So, this really is kind of a change that you are seeing a little bit with the, like you said, increase in diabetes and just the poor health to begin with.

Dr. ZIEVE. Yes.

Mr. BOOZMAN. Good enough.

You mentioned the metabolic syndrome several times, and this really was not something that we had heard about until the last few years. Now we have a whole clinic, you know, devoted to it. What is the deal with that?

Dr. ZIEVE. Actually, this has an interesting history. I think you could probably trace the concept back to the Bronx VA hospital in 1958 when Berson and Yallow developed the ability to assay the plasma insulin level and for which Yallow later got the Nobel Prize—Berson had died prematurely of a coronary before that—and they took a group of Type 1 diabetics and found that their circulating insulin level was zero.

They took a group of Type 2 diabetics, expecting it to be low, and found that their insulin level was higher than it was in normals. So, obviously, insulin was not working right.

That was the first indication that there was a problem with insulin resistance, and subsequently, over the last several years, as obesity has become more of a problem, as diabetes has become more of a problem, it has become recognized that the pre-diabetic

state is also a group of people who are at tremendously high coronary event risk, and that is a group that is getting bigger every year.

So both the NIH, the National Cholesterol Education Project, and the World Health Organization, within the past five years, have defined criteria for identifying the metabolic syndrome people, and our feeling is these are the people who have the heart attacks, that is where our prevention efforts ought to be focused.

Mr. BOOZMAN. One other thing. I know in the—I am from Arkansas, and the VA in Little Rock has a really good program where they have the ability to screen retinas, you know, from other—in other words, you know, a practitioner can see something that they are really not sure about. Rather than make that person take a trip to Little Rock, you know, they can scan the image, you know, retinal photography, and then somebody there read all of those.

Is that the type of thing that we need to be doing more of in the VA system?

Dr. ZIEVE. Yes. Yes, I think it is, and in the general community, too, but it is going to be easier to do it in the VA because of telemedicine hookups that are possible. I think this sort of thing is tremendously valuable in picking up early disease, because basically nobody should ever go blind from diabetic retinopathy.

First of all, with meticulous control from the start, the retinopathy is preventable, and even when you get it, laser surgery is tremendously effective at preserving vision if you know about it early enough.

Mr. BOOZMAN. Thank you very much.

Mr. BUYER. It is kind of unusual to go to a third round. I still have questions.

Ms. HOOLEY. I have just one.

Mr. BUYER. Go ahead, Ms. Hooley.

Ms. HOOLEY. No, go ahead. You are first.

Mr. BUYER. No, go ahead. You are eager. You are ready to go.

Ms. HOOLEY. All right.

Are there any applications of the deep brain stimulation that we use for Parkinson's that can be used in treating Alzheimer's patients? Is there any research on that? Anyone of you, anyone in the room. I do not care.

Dr. SANO. Many of the areas that we know are important in Alzheimer's disease for better neuron communication are also areas that have potential for having seizures, and so, the model of brain stimulation in Alzheimer's disease is not really well developed, for that reason, because those many cortical areas are areas that, if stimulated, are more likely to be associated with side effects, such as seizure.

Ms. HOOLEY. Okay. Thanks.

Dr. FERRANTE. I think equally important is that there is primarily one brain area involved in Parkinson's disease, where it is multi-factorial in Alzheimer's, with many sub-cortical as well as cortical areas that are involved in Alzheimer's disease. So, in order to select out one in Alzheimer's disease would be very difficult to do.

Mr. BUYER. I would like to go back to the—with regard to VA research and the top 10 conditions—and I want to make sure

whether or not this is fair or not for me—when I look at the list of the top 10 for which you had testified, is it fair to say that, when I look at the dollar amount and—if I were to put them in a declining scale on dollars, is it fair to say that this would then be the priority of the VA with regard to your research budget? So, when you say mental health, 220 million; cancer, 157 million; heart disease, 81.9 million; aging, 71.2 million; substance abuse, 59.4 million, etcetera, is it fair to say that I link dollars to priorities or not?

Dr. KUSSMAN. I do not think there is necessarily a direct correlation with that, to be honest.

Clearly, these are disease entities that are important to us in the treatment of the veterans, and so, clearly, as you can see from the numbers that were listed, mental health research was number one. It's clearly serious, the mentally ill, and other—drug and alcohol and other issues related to that are very important to the VA, as well as cancer and heart disease and aging.

So I don't think it is a mistake that these are near the top, but I would not go so far to say that they were prioritized in any particular way that mental health was considered number one versus cancer or heart disease.

Mr. BUYER. So it would not be fair to link a dollar amount with regard to a particular condition as a barometer with regard to your priorities?

Dr. KUSSMAN. I believe that that would be a fair statement, sir.

Mr. BUYER. Okay.

Do you, within the research arena—do you prioritize? Do you say one through five or one through 10?

Dr. O'LEARY. Unfortunately, Mr. Chairman, I am relatively new to this position, and I cannot speak to the history. What I can say is that we are actively reviewing the portfolios now to understand the relationships better. We have conducted some preliminary reviews, but we also remember as we are doing this that we have some special populations of veterans that we have been asked to give special consideration to in our research funding priorities, and these include things like prosthetics, spinal cord injury, rehabilitation, Gulf War research, and so, these kinds of things will have an influence because of the special role of VA in some of these areas that differs substantially from that of the NIH or others in making their funding allocations.

Mr. BUYER. Thank you.

This is only my opinion; it is not the opinion of others. When Congress doubled the NIH budget to push the bounds of science to betterment of our society, we recognize that you have been a great influence upon other research throughout the country. There is a multiplier effect of that and a stimulus that goes into the private sector, which then comes back around, it is almost circuitous. What I am most hopeful about is that that impact of that five-year investment does not de-focus the VA with regard to its veteran-centric research priorities.

Now, that is just my opinion, so I cannot speak for the committee. So that is the reason I asked this particular question.

So are you in discussions or have you also noticed to make sure that veteran-centric priorities with regard to all population is extremely important and that we are not de-focused, yet we recognize

that our research can have attributes to the betterment of our society, but let us not de-focus the purpose of the VA research. Would you concur or not concur and comment, please?

Dr. KUSSMAN. Yes, sir. I think that that is what Dr. O'Leary was alluding to, re-evaluating and assessing and being sure that we don't lose focus on things that are particularly important to the veteran.

As you know from the discussion and other things, there is a tremendous overlap with—things that are important to the VA are clearly important to society, as well, but as mentioned, there are some things that are fairly unique to the VA patient population that we would like to emphasize.

Mr. BUYER. Something I thought was rather interesting, sort of a side note—one of the benefits of being on the health subcommittee of Commerce—Dr. Zerhouni, if I pronounced that right—when he came and testified and we talked about sexually transmitted diseases, there is a—I forgot the word he used to describe it—80 million Americans—80 million—80 million Americans have been exposed to sexually transmitted diseases in a country of 300 million—oh, epidemic, a public health epidemic. It is pretty stunning when you think about, okay, all of our research and what we are doing and where we focused, yet with regard to sexually transmitted diseases—I am not talking strictly AIDS—venereal diseases and herpes, et cetera—but when I went and looked at the VA, then, in this whole question about centric research and veterans, interesting input from the VA—and you could comment or not, Dr. Kussman—is that, with regard to sexually transmitted diseases, total funding for fiscal year 2003 was 985,000 for 14 projects.

In comparison, there were almost 8,200 total patient visits in fiscal year 2003 for sexually transmitted diseases out of almost 50 million total patients' visits. It is interesting.

So here is a prime example of numerator and denominator, everything just all of a sudden flipping, society having a major problem, public health epidemic, with regard to NIH.

Tell one of your comrades over there to open up their eyes—or colleagues—open up your eyes with regard to funding priorities for a public health epidemic. Yet, within our veterans population, we are not having the equivalent epidemic.

So I only bring this up as we are trying to—I am trying to pay attention with regard to our population versus what is happening also in society's population with regard to our limited dollars and how we invest. That is why we asked you to come here today with regard to aging diseases for the collaborative efforts, but yet we do not want to be de-focused.

Do you see what I am trying to say? Do you concur with what I have just said, Dr. Kussman?

Dr. KUSSMAN. Yes, sir.

Mr. BUYER. All right.

The last thing I have, with regard to the—Dr. Salerno, your experts who are here—if they could please provide some testimony right now—let us know what are the cutting edge project that you are working on, clinical trial that you are so excited about you cannot wait to get out of your chair and tell us about with regard to the three diseases.

If you could slide over, Dr. Salerno, and let someone have a seat.

Dr. MURPHY. I am Diane Murphy from the National Institute on Neurological Disorders and Stroke, and one of our more exciting trials you have already heard a lot about today, which is the collaborative trial on DBS between the Veterans Administration and our institute, but we have also started a trial to test neuroprotectants in early stages of Parkinson's disease, and Ms. Hooley actually questioned a little bit about this earlier.

The idea of the trial is to pilot some drugs that may delay the progression of disease or retard the progression of Parkinson's disease so that patients can stay in a manageable state for much longer, and we have funded 51 sites around the country, and we are going to be testing—piloting right now drugs like creatine and co-enzyme Q, any drugs which have shown promise in acting as neuroprotectants, and at the end of this pilot period, one of those drugs will be selected for a large-scale clinical trial.

Mr. BUYER. Next? We have six minutes to do this.

Dr. FRADKIN. I think that there has been an explosion of knowledge——

Mr. BUYER. Identify yourself for the record.

Dr. FRADKIN. I am Judy Fradkin from the National Institute of Diabetes and Digestive and Kidney Diseases. You heard from Dr. Zieve about some of the research that the Richmond VA Hospital have been doing on leptin. This is a piece of the larger explosion of research that has been going on with regard to understanding the biologic basis of appetite regulation, and of control of metabolism and responsiveness to insulin. All of these processes are integrated by a whole new series of chemical messengers that have really just begun to be identified.

This creates tremendous opportunity in terms of developing targets for drug discovery and new therapeutics.

As this hearing has emphasized, prevention is key for diabetes. Obesity is a major contributor to diabetes risk. We have, on the one side, a very successful trial of lifestyle interventions that have been shown to be very effective in preventing or developing development of diabetes.

On the other hand for people who aren't able to change activity and diet—and this is difficult in an environment that promotes obesity and a sedentary lifestyle—we now have a whole new series of potential biologic targets that may help us develop other kind of therapeutic interventions.

Mr. BUYER. Thank you.

Next?

Dr. MORRISON-BOGORAD. One of the major things which I think is most promising in Alzheimer's disease research is trying to stop cell death and stop the loss of connections between nerve cells that actually seems to relate most closely to loss of cognitive function, and there are a number of avenues of research that actually cross a number of neurodegenerative diseases which are focusing on the accumulation of the abnormal proteins in Alzheimer's disease and Parkinson's and how this can be stopped.

There are a number of ways this is really being looked at, and one is in Alzheimer's, to stop the accumulation of the amyloid protein and its deposition into plaques, and so, we have, through ge-

netic research and basic molecular research, a tremendous understanding how of the pathways through which plaques are generated, and there are perhaps six or eight targets, now that we know these pathways, where researchers are working to stop plaques being formed or to remove them once they have been formed.

One avenue which took quite a setback a couple of years ago but which I think is extraordinarily promising is the vaccine approach that you probably heard about, where a clinical trial had a problem in that the vaccine of amyloid did create neurological complications in some of the people in the trials, and so, the trial was stopped, but what researchers are back doing now is to try to find a safer way of vaccinating the person against amyloid so that the plaques will be removed.

Another very important line of research is perhaps a little bit simpler, and that is one of the essences of our approaches, is, one, to look at very complicated ways of stopping the disease, developing new drugs, developing new compounds.

Another is to go back to epidemiology studies and see whether something as basic as antioxidants in the diet might help slow the development of the disease, as well as perhaps slow aging, as well, and we have a number of very promising studies in rodents and also in dogs which suggest that antioxidants really slow development of cognitive decline, and so, these perhaps are two of the most promising areas that I would like to tell you about.

Mr. BUYER. That is great. Thank you very much.

I would like to thank my colleagues for their contributions. I would like to thank NIH and the VA for being here. These are very important collaborative efforts which you have ongoing.

Dr. Kussman, if I would note, the subcommittee held a hearing on September 19th of 2002 on VA research and research foundations. At the time, I had asked the Under Secretary how many affiliated universities had signed cooperative agreements in what is commonly called the cooperative technology administration agreements, which we had referred to earlier. At the time, Dr. Roswell stated that such notable universities as Yale, Duke, Emery, University of Michigan, had not established these agreements. I had asked for the funding stream over the last 10 years of the top universities. They ranged at close to $100 million between NIH and the VA.

So I take, for example, Duke University. With regard to Duke, this effort to sign these agreements started in 2000, and we got a copy of a letter just signed yesterday to the committee from Duke University saying, well, we are still working on it.

I would like for somebody to come over and brief the committee, this subcommittee, with regard to an update with regard to getting these agreements signed with these universities, all right?

Dr. KUSSMAN. Yes, sir.

Mr. BUYER. All right. Thank you very much.

The hearing is now concluded.

[Whereupon, at 12:00 p.m., the subcommittee was adjourned.]

APPENDIX

Testimony
Before the Subcommittee on Oversight and Investigations
Committee on Veterans Affairs
United States House of Representatives

RESEARCH ON ALZHEIMER'S DISEASE, PARKINSON'S DISEASE AND DIABETES AT THE NATIONAL INSTITUTES OF HEALTH

Statement of

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National Institutes of Health
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 10:00 am
on Wednesday, April 28, 2004

Chairman Buyer and Members of the Subcommittee:

Thank you for inviting me here today to discuss three devastating diseases that disproportionately affect older Americans: Alzheimer's disease (AD), Parkinson's disease (PD), and diabetes. I am Dr. Judith Salerno, Deputy Director of the National Institute on Aging (NIA). Since the NIA is the lead Federal agency for AD research, I will be discussing a number of recent advances and ongoing activities in this area. With me to discuss the status of AD research is Dr. Marcelle Morrison-Bogorad, Director of the NIA's Neuroscience and Neuropsychology of Aging Program. I will also discuss ongoing Parkinson's disease and diabetes research at the National Institutes of Health (NIH). Dr. Diane Murphy, Program Director for Neurodegeneration at the National Institute of Neurological Disorders and Stroke (NINDS) and Dr. Judith Fradkin, Director, Division of Diabetes, Endocrinology and Metabolic Diseases at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) are also here today to answer any questions you may have about these research areas.

According to the U.S. Bureau of the Census, there are currently 26.4 million veterans of the armed forces in the United States, 37 percent of whom are over age 65, compared to 13 percent of the total U.S. population. The Veterans' Health Administration estimates that the number of "oldest old" veterans – those age 85 or older – will peak in 2012 at 1.4 million, representing an increase of 167 percent over 2000 levels. As with the general population, these older individuals are vulnerable to diseases and conditions of aging, including AD, PD, and diabetes. The magnitude of the older veteran population, however, gives particular urgency to issues related to the prevention and treatment of such age-associated conditions for those who care for our veterans.

Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder that starts slowly with a mild loss of memory but progresses relentlessly until it destroys one's ability to carry out even the simplest tasks. Causing this mental decline is an inexorable buildup of brain changes – insoluble deposits called plaques and tangles that accumulate in particular brain regions, damage from inflammation and oxidative stress, loss of connections

between nerve cells in memory and other pathways, and eventual death of these brain cells. AD's impact on individuals, families, the health care system, and society as a whole is profound: Approximately 4.5 million Americans currently have AD, with annual costs for the disease estimated to exceed $100 billion.[1] Moreover, the rapid aging of the American population threatens to increase this burden significantly in the coming decades. Demographic studies suggest that if current trends hold, the annual number of incident cases of AD will begin to sharply increase around the year 2030, when all the baby boomers (born between 1946 and 1964) will be over age 65. By the year 2050, the number of Americans with AD could rise to some 13.2 million, an almost three-fold increase.[2]

But these numbers, however stark, do not tell the whole story. Although AD remains a major public health issue for the United States, we have made, and are continuing to make, dramatic gains in our ability to understand and diagnose AD that offer us the hope of preventing and treating the disease. Our efforts against AD have been greatly enhanced through the involvement of veterans and the research scientists of the Veterans Health Administration. For example, many NIH-supported Alzheimer's researchers hold VA appointments, and veterans themselves participate in a number of AD research studies. In addition, many of the major advances in understanding AD have come from work at the 29 NIA-supported Alzheimer's Disease Centers (ADCs) across the country, at which multidisciplinary research teams focus on the disease. Several of the ADCs are located at VA medical centers, including major programs in the Bronx, New York; Bedford, Massachusetts; Puget Sound, Washington; and Palo Alto and Martinez, California. Other ADCs, while not directly affiliated, have close ties with local VA centers – for example, collaborating on research projects or recruiting veterans for participation in clinical studies. Partnerships with VA researchers have strengthened our search for ways to delay and, ultimately, to prevent the devastation of this disease.

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[1] Data from the Alzheimer's Association. See also Ernst, RL; Hay, JW. "The U.S. Economic and Social Costs of Alzheimer's Disease Revisited." *American Journal of Public Health* 1994; 84(8): 1261 – 1264. This study cites figures based on 1991 data, which were updated in the journal's press release to 1994 figures.

[2] Hebert, LE; Scherr, PA; Bienias, JL; Bennett, DA; Evans, DA. "Alzheimer Disease in the U.S. Population: Prevalence Estimates Using the 2000 Census." *Archives of Neurology* August 2003; 60 (8): 1119 – 1122.

Risk Factors

The risk of AD increases dramatically with age, with nearly half of all individuals over age 85 being affected.[3] Many older Americans struggle with mild cognitive impairment (MCI), a condition that is frequently a precursor to AD; in one recent population-based study of cognition in the elderly, 22 percent of participants over 75, and 29 percent of those over 85, were diagnosed with MCI.[4] Determining who is at high risk of developing AD and who is not – and why -- will enable us to identify potential targets for preventive intervention, as well as those individuals who might benefit most from such interventions.

Through laboratory, clinical and population-based research, we have identified a number of risk factors for AD, including both genetic and lifestyle factors. We already know three major gene mutations on Chromosomes 21, 14, and 1 are associated with early-onset disease – one of which was identified by a VA investigator, with NIA and VA support. Another gene, ApoE4, has been identified as a major risk factor for the more common late-onset disease. Recent findings are enabling us to close in on several others, thought to be on chromosomes 9, 10, and 12. The NIA's AD Genetics Initiative, the goal of which is to develop strategies for rapidly identifying the additional late-onset AD (LOAD) risk factor genes, associated environmental factors, and the interactions of genes and the environment, has already enrolled over 200 families or approximately 600 participants in its first year.

Recently, neuroscientists have become increasingly interested in a specific set of genes that may influence not whether, but when, a person might develop symptoms of neurodegenerative disease. Delaying the onset of AD symptoms by even five years could greatly reduce the numbers of people who will have the disease, as well as providing additional cognitively-healthy time to those who will eventually be diagnosed.

Recently, NIH-supported investigators found a gene on chromosome 10 that they believe influences the age of onset of both Alzheimer's disease and Parkinson's disease.

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[3] Data from the Alzheimer's Association. See also Evans, DA; Funkenstein, HH; Albert, MS; et al. "Prevalence of Alzheimer's Disease in a Community Population of Older Persons: Higher than Previously Reported." *JAMA* 1989; 262(18): 2552 – 2556.

[4] Lopez O, Jagust WJ, DeKosky ST, Becker JT, et al. "Prevalence and Classification of Mild Cognitive Impairment in the Cardiovascular Health Study Cognition Study." *Arch Neuro* 60: 1385-1389, 2003.

Using a novel method to match the genes of people affected with these diseases with the age at which study participants started developing symptoms, the scientists found that one gene, GSTO1, was significantly associated with late onset of both Alzheimer's and Parkinson's. This important work gives us new clues to the role of genetics in the timing of late-life forms of these devastating neurodegenerative diseases.

Not only genetic but also lifestyle factors may influence risk of AD. For example, epidemiological studies, including one undertaken by NIA's intramural program involving veterans with head injuries sustained while on active duty during World War II, suggest that head injury may be a long-term risk factor. Other conditions such as heart disease, high blood pressure, and stroke may also increase risk. We are currently supporting several studies to determine whether treating these conditions will delay the onset of AD.

Type 2 diabetes is another potential risk factor for cognitive decline and AD. In a recent study, researchers found that compared to older non-diabetic women, older women with type 2 diabetes were about 30 percent more likely to score poorly on tests of cognitive function, and the risk increased with the duration of their condition. However, the diabetic women in the study who took glucose-lowering pills had a risk similar to non-diabetic women. Recognizing the potential link between type 2 diabetes and cognitive decline, NIH -supported researchers with funding from NIA and NIDDK are currently participating in an offshoot of the National Heart, Lung, and Blood Institute's Action to Control Cardiovascular Risk in Diabetes (ACCORD) study. ACCORD evaluates whether more intensive glucose, blood pressure and lipid management can reduce cardiovascular disease in people with diabetes; the aim of this sub-study, ACCORD-MIND, is to test whether the rate of cognitive decline and structural brain change in people with diabetes who are treated with standard care guidelines is different than in people with diabetes treated with intensive care guidelines. We anticipate that 2800 people will participate in ACCORD-MIND.

Imaging

Powerful imaging techniques, including positron emission tomography (PET) and magnetic resonance imaging (MRI), are opening a window into the living brain, allowing us to visualize not only anatomical structures but also functional processes and activities

at the molecular level. The refinement of these techniques continues to have a profound effect on all areas of neuroscientific research. In fact, improvements in brain imaging, coupled with the development of more sensitive cognitive tests, are enabling us to diagnose AD in the research setting with greater precision than ever before. While there remains no scientifically validated method to visualize AD's pathological hallmarks - amyloid plaques and neurofibrillary tangles - in a living human, researchers have recently developed the first radiotracers, including a molecule called Pittsburgh Compound-B, that facilitate visualization of amyloid deposition in living AD patients using PET scans. Although further research is needed, these molecules may eventually offer us a powerful and accurate tool for the early diagnosis of the disease.

Advances in imaging also have the potential to enable us to visualize the effects of therapeutic interventions more rapidly and accurately, with the potential for making AD clinical intervention trials smaller, faster and more affordable. Finding a biological way to accurately track AD development and progression is one of the objectives of the NIA's Neuroimaging Initiative, a large-scale partnership among NIA/NIH, academic investigators, the pharmaceutical and imaging equipment industries, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, and the NIH Foundation, with participation from the Alzheimer's Association and the Institute for the Study of Aging. This initiative is slated to begin this year.

Prevention and Treatment

NIA is currently supporting 25 AD clinical trials, including large-scale prevention trials, which are testing agents such as hormones, anti-inflammatory drugs, statins, homocysteine-lowering vitamins, and anti-oxidants for their effects on slowing progress of the disease, delaying AD's onset, or preventing the disease altogether. Other intervention trials are assessing the effects of various compounds on the behavioral symptoms (agitation, aggression, and sleep disorders) of people with AD. As imaging and laboratory studies reveal more about AD's pathology, we are identifying a number of novel molecular characteristics that may prove to be targets for future treatment of the disease.

Disseminating information about prevention and treatment of AD, as well as general information about the disease, is the mission of the NIA's Alzheimer's Disease Education and Referral Center (ADEAR). Serving AD patients and their families, health professionals, and the general public alike, ADEAR staff answer questions about the disease, provide free publications, and offer referrals to local supportive services and AD Centers specializing in diagnosis and treatment. In 2003, ADEAR distributed over 675,000 free publications, and there were over 1.5 million unique visitors to the ADEAR website (http://www.alzheimers.org/).

Caregiving

Most of the over 4 million Americans with AD today are cared for outside the institutional setting by an adult child or in-law, a spouse, another relative, or a friend. Caregiving issues are of great importance, since perhaps one of the greatest costs of AD is the physical and emotional toll on caregivers. Our major clinical trial on effective caregiver interventions, Resources for Enhancing Alzheimer's Caregiver Health (REACH), is funded jointly by the NIA and the National Institute of Nursing Research. One of the REACH sites is located at the Veterans Affairs Palo Alto Health Care System, a leading center in aging research. Now in its follow-up phase, REACH II, the study uses a multi-component intervention comprising the most effective interventions identified in REACH I. The intervention targets five areas – safety, self-care, social support, emotional well-being, and patient problem behaviors – and holds promise for alleviating the enormous burden of caregivers of Alzheimer's victims.

Parkinson's Disease

Background and Planning Efforts

Like AD, Parkinson's disease (PD) is also a devastating and debilitating neurological disorder; however, it is caused by the progressive loss of nerve cells that control movement. These cells produce the neurotransmitter dopamine, and their loss leads to tremors, rigidity, and slowing of movement. Other disabling symptoms can also occur, including speech problems and, in some individuals, difficulties with thinking, sleep, and depression. PD affects more than 500,000 Americans at any given time, and

its severity varies from person to person. We are fortunate that most patients can be treated successfully with the drug L-dopa, one of the most effective treatments available for any neurological disorder. However, many people become severely disabled, either when L-dopa loses its effectiveness or when increasing doses lead to debilitating side effects. The costs of this treatment and disability are believed to reach $6 billion[5] annually in the United States, making both treatment and prevention high research priorities. Though PD is diagnosed in some people younger than 50, it remains primarily a disease of aging, and for this reason, will continue to be an important health consideration for our veterans.

For more than three decades, the National Institute of Neurological Disorders and Stroke (NINDS) has been active in PD research, supporting early studies of L-dopa, fundamental research on the brain circuitry affected by PD, the development of critical animal models, and important advances in understanding the genetic basis of parkinsonism. In recent years, advances in areas of basic neuroscience, such as genetics, stem cells, natural growth factors, and brain circuits, have opened new opportunities to understand what causes PD and to develop improved treatments even for people with advanced disease. To exploit these opportunities, and ensure that public health needs are addressed, NINDS has led a large planning effort in PD research for the past four years, on behalf of the NIH.

The core of the NIH PD planning effort is the Parkinson's Disease Research Agenda, a five-year plan developed in March 2000 that provides a comprehensive overview of the research needed to understand the causes of PD and move forward with the development of treatments. NIH was already active in all of these research areas when the Agenda was created, and the Agenda identified several emerging opportunities for the NIH to pursue with greater emphasis.

The second phase of these planning efforts was initiated in July 2002, when NIH Director Elias Zerhouni convened a "Summit" with a small group of outstanding scientists to gain a better sense of where the field of PD research stood at the global level,

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[5] DHHS/NIH Disease-specific Estimates of Direct and Indirect Costs of Illness and NIH Support Report, FY2000 Update, citing Lierman, T.L., *Building a Healthy America*, 1992, 2nd ed., (Mary Ann Liebert, Inc.)

and to identify potential impediments to progress. The NIH developed the recommendations from the Summit into a matrix that outlined short-to-long range and low-to-high risk goals that address these roadblocks; a number of the short-term goals have been met already.

One of the core features of the 2002 PD Summit is the development of goals in the context of the research that is being supported by other Federal partners and private funding organizations. NINDS is currently tracking the NIH portfolio of PD research, along with the grants funded by the VA, the Department of Defense (DoD), and private foundations; today, staff monitor more than 1000 PD research projects. Through these analyses, regular discussions with VA and DoD staff, and meetings of the Federal-wide PD Coordinating Committee, NINDS and many other NIH Institutes continue to explore ways to facilitate collaboration.

Program Highlights and VA Collaborations

The clinical testing of promising treatments for PD remains a high priority. To address this, the NINDS developed the PD Neuroprotection Trial, or NET-PD, which will expedite the selection and testing of drugs that might slow or stop the progression of PD. In most clinical trials funded by the NINDS, investigators select the drugs and design the trial. By contrast, for NET-PD, NINDS first solicited suggestions for promising drug candidates from academia, industry, and voluntary health organizations, both here and abroad. Then, a team of clinicians, pharmacologists, and clinical trial experts, including NINDS scientific staff, evaluated the 59 compounds that were nominated. While the drug selection process was underway, the NINDS created a network of 42 (now 51) clinical sites around the country, including one that will recruit subjects at the Ann Arbor VA Medical Center; set up independent coordination and statistical centers; and designed the early phase clinical trials. The trial sites have already completed recruitment of people with early, untreated PD to participate in phase II clinical trials of the first two drugs selected by this process. Enrollment for trials of the next two agents is underway.

Surgical therapies for PD are also promising, particularly for individuals in advanced stages of the disease. To address this need, NINDS and the VA initiated the largest trial of deep brain stimulation (DBS) for PD to date in January 2002. DBS

involves the passage of electrical current through electrodes that are surgically implanted in very specific brain regions that are critical to motor control. The trial was designed to enroll over 300 subjects at multiple VA sites and affiliated academic institutions, and researchers will compare stimulation of two different brain regions to best practices in the medical management of Parkinson's. If DBS is shown to be the more effective approach, subjects on standard management will also receive DBS – and the effects of the two different stimulation strategies will be compared. The trial is progressing well, with over half of the needed participants recruited already, and the results are expected to have an important influence on the management of PD.

In addition to these two strategies, gene therapy may provide a third approach to treating PD, and NINDS is committed to moving as rapidly as is prudent toward human testing. In October 2000, the NINDS sponsored a scientific workshop on "Gene Therapy for Neurological Disorders." As a consequence of this meeting, several researchers formed a working group to address PD gene therapy in a concerted fashion and are conducting extensive development and testing of gene therapy strategies in animal models of PD. The NINDS oversight of this project uses milestone-driven funding, as is common in industry, and the first-year milestones were accomplished on schedule.

In the future, NINDS will continue to track the research in PD that the VA is supporting, and look for opportunities for collaboration wherever possible. The continued inclusion of the VA in efforts such as the PD Coordinating Committee will ensure that these efforts are productive for veterans and for all Americans.

Diabetes

Diabetes is a major – and escalating – public health problem in the United States. The sixth leading cause of death, diabetes lowers average life expectancy by up to 15 years. It is the leading cause of kidney failure, lower limb amputations, and adult-onset blindness, and adults with diabetes have heart disease death rates two to four times higher than those without diabetes.

Six percent of the population – some 18.2 million Americans – currently has diabetes; 90 to 95 percent of these people have type 2 (formerly called "adult onset")

diabetes. About 1.3 million people are newly diagnosed with diabetes each year, the great majority of whom are 40 years of age or older. Disturbingly, nearly one-third of Americans with diabetes are unaware that they have the disease and are thus not taking the steps proven effective in reducing its complications. The estimated total financial cost for diabetes in the U.S., including costs of medical care, disability, and premature death, was $132 billion in 2002, up from $98 billion in 1997.[6]

Type 2 diabetes is associated with several risk factors, including older age and a family history of the disease. It is also strongly associated with obesity: more than 80 percent of people with type 2 diabetes are overweight or obese. Of Americans 60 and older, about 8.6 million, or 18.3 percent, have type 2 diabetes. Type 2 diabetes also occurs more frequently among certain racial and ethnic groups, including African Americans, Hispanic Americans, American Indians, and Native Hawaiians.

Preventing diabetes is the key to controlling the growing diabetes epidemic, and this is reflected in the NIH's program emphasis. For example, results of the recently completed Diabetes Prevention Program (DPP), a national clinical trial led by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in collaboration with other NIH Institutes, demonstrated that individuals at substantial risk of developing type 2 diabetes could prevent or delay disease onset and improve their blood sugar levels through modest improvements in diet and exercise. This was the first major clinical trial to show that improvements in diet and exercise can be effective in reducing diabetes in a diverse population of at-risk people. NIH is conducting follow-up studies of the DPP participants to determine the durability of the DPP interventions, as well as studying the long-term effect of the interventions on the development of complications.

To promote translation of the DPP results into real health improvement for the American people, the NIDDK and the Centers for Disease Control and Prevention (CDC) recently developed the first national diabetes prevention campaign, "Small Steps. Big Rewards: Prevent Type 2 Diabetes." This program includes a toolkit for health care providers based on methods used in the DPP and a "game plan" for those with pre-

[6] Statistics from the National Diabetes Information Clearinghouse, http://diabetes.niddk.nih.gov/dm/pubs/statistics/.

diabetes, with a calorie counter and tips on how to set goals, track progress, and start a walking program. The message is that by losing a modest amount of weight, getting 30 minutes of physical activity five days a week, and eating healthier, people with pre-diabetes can delay or prevent the onset of the disease.

The "Small Steps. Big Rewards" campaign is part of the larger NIDDK-CDC National Diabetes Education Program (NDEP). Another NDEP health awareness campaign, "Be Smart About Your Heart: Know the ABCs of Diabetes," is aimed at helping people with diabetes and their health care providers to better understand the need to control all aspects of their diabetes to help prevent heart attacks or strokes. The NDEP is also participating in Health and Human Services Secretary Thompson's "Diabetes Detection Initiative (DDI): Finding the Undiagnosed," which is an effort to identify individuals at high risk for undiagnosed type 2 diabetes, and then refer them for initial screening in a clinical setting and follow-up care, if needed.

The NIDDK heads the Diabetes Mellitus Interagency Coordinating Committee (DMICC), which is charged with coordinating the diabetes research activities of all Federal programs, including the NIH and the VA, that are related to diabetes and its complications. Recent DMICC meeting topics have included leveraging the NIH investment in obesity research to enhance research and care for diabetes; jointly-funded (NIDDK/VA) research on the role of specialized footwear in preventing diabetic foot ulcers; and a new program called "MOVE" (Managing Overweight and Obesity among Veterans Everywhere), which was developed by the VA National Prevention Center with assistance from NIH scientists and is being piloted at 17 facilities.

The NIDDK and the VA also work together on the National Diabetes Quality Improvement Alliance, a collaboration of 13 private and public national organizations dedicated to the improvement of adult diabetes care.

In addition, the NIDDK supports studies of approaches to translate important advances from clinical trials in diabetes prevention and care into medical practice. Some approaches are targeted at improving care for specific populations, such as a low-income Latino population. Others study specific settings, such as a clinic serving inner city African Americans, or an interactive video conferencing system to connect health professionals at a large medical center with rural diabetes patients with limited access to

health care providers. The NIDDK and VA are collaborating on the CDC-led "Translating Research into Action for Diabetes" (TRIAD) study, which is examining the efficacy and cost-effectiveness of approaches to improve the quality of diabetes care, quality-of-life, and health status for people with diabetes in managed care settings. The VA has used the CDC TRIAD protocol to conduct a parallel study within VA sites that are geographically proximate to CDC TRIAD sites. Success in these trials could pave the way to widespread use of these interventions in communities throughout America.

Conclusion

As our population rapidly grows older, it is ever more urgent that we find effective ways to address diseases and conditions such as AD, PD, and diabetes that are associated with advanced age. Although we have made a number of important advances in the past few years, much work remains in each of these areas. By continuing and intensifying research, we can move forward in meeting the promise of a healthy old age by improving the health and well being of our veterans – and all Americans.

Statement
of
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Acting Deputy Under Secretary for Health
Department of Veterans Affairs
on
VA Research on Alzheimer's Disease, Diabetes, and Parkinson's Disease,
before the
Subcommittee on Oversight and Investigations
of the
Committee on Veterans' Affairs
U.S. House of Representatives

April 28, 2004
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Mr. Chairman and Members of the Subcommittee, I appreciate the opportunity to appear before you today to discuss the Department of Veterans Affairs' (VA) research into Alzheimer's disease, diabetes, and Parkinson's disease. VA research is committed to better understanding the causes and developing treatments and preventive measures for these diseases. Today, I would like to discuss the many achievements of VA research to help achieve this end.

Parkinson's Disease

Parkinson's Disease is a slowly progressive disorder that results from the degeneration of nerve cells in a small area of the midbrain that use the chemical dopamine to transmit information to other brain regions. Symptoms include tremors, slowness of movement, stiffness of the limbs, and problems with gait or balance. The symptoms interfere with employment and normal activities of daily living. The disease affects more than 500,000 Americans. The prevalence of Parkinson's disease increases with age; it affects 1% of the U.S. population over age 60 and 3.4% over age 74. Progress towards understanding the cause and cure of Parkinson's disease is crucially important to the population of aging veterans. Parkinson's disease affects thousands of veterans and creates an enormous burden on patients and their families. VA medical centers treat over 40,000 Parkinson's disease patients every year. At present there is no cure for Parkinson's disease, but treatments do exist and are

available. Despite advances in treatment, relentless progression of neuronal damage frequently leads to total disability. Further research into fundamental mechanisms of neuronal degeneration is the best hope for the development of improved diagnostic and treatment regimens.

The four Research Services of VA's Office of Research and Development, Biomedical Laboratory Research & Development Service (BLR&D), Clinical Science Research & Development Service (CSR&D), Health Services Research & Development Service (HSR&D), and Rehabilitation Research & Development Service (RR&D), have made funding for innovative studies focused on the pathogenesis and treatment of Parkinson's disease a high priority. Over the past five years, VA funding for Parkinson's disease research has nearly doubled, with $10.1 million allocated for projects in FY 2004. Since FY 1999, non-VA funding has more than doubled, with VA investigators leveraging over $6.4 million in non-VA funds in FY 2003. The funded projects focus on various aspects of Parkinson's disease research, including:

- the role of neurotransmitters other than dopamine,
- advances in neuroimaging technologies to monitor disease progression,
- stem cell and fetal transplantation research in animal models,
- gene therapy in animal models,
- mechanisms of damage to nerve cells,
- non-motor aspects of Parkinson's disease,
- rehabilitative strategies for Parkinson's disease, and
- clinical trials of surgical treatment for refractive Parkinson's disease.

With the development of six Parkinson's Disease Research, Education and Clinical Centers (PADRECCs), initiated in FY 2001, VA took a major step toward improving patient care and outcomes while, over the longer term, pursuing a cure for Parkinson's disease. Operating together as a national consortium, the PADRECCs conduct research covering basic biomedicine, rehabilitation, health services delivery, and clinical trials. Each Center is participating in a landmark clinical trial with the Cooperative Studies Program (CSP) that began in November 2001 to assess the

effectiveness of surgical implantation of deep brain stimulators (DBS) in reducing the symptoms of Parkinson's disease.

In collaboration with the National Institutes of Health's (NIH) National Institute for Neurological Disorders and Stroke, the DBS trial on Parkinson's disease is investigating a promising neurosurgical technique utilizing implantation of electrical stimulation devices, in comparison to best medical therapy, to assess the impact on symptoms and functioning of Parkinson's patients. This study will be the largest trial to assess the effectiveness of DBS to treat refractory Parkinson's disease. There are two components to this study, a comparison of best medical therapy to DBS, and a comparison of stimulation at two locations on patient outcomes (simultaneous bilateral subthalamic nuclei stimulation (STN) and simultaneous bilateral globus pallidus (GPi) stimulation). The objective of the "stimulation" component, assessed at two years following surgery, is to determine at which location is stimulation more effective in attenuating symptoms of Parkinson's disease at the end of the two-year period. The objective of the "medical therapy" component is to determine whether DBS or best medical therapy is more effective at six months in improving Parkinson's disease motor symptoms. The primary study endpoint for comparison of surgical site (STN vs. GPi DBS) is a widely accepted standard clinical scale for evaluating individuals with Parkinson's disease (the motor subscale of the Unified Parkinson's disease Rating Scale). For the comparison of best medical therapy to DBS, the primary endpoint will be time spent without having difficulties in performing voluntary movements on patient motor diaries. The study is planned to continue until 2007. As of April 2004, 138 patients have enrolled.

In addition to the DBS trial, the PADRECCs are implementing a prospective patient care registry as a means of monitoring the care of veterans. No such clinical Parkinson's disease registry has been previously established on a national scale. The anticipated benefits are the improvement of clinical care by tracking the clinical status and interventions of veterans with Parkinson's disease. The PADRECCs were also recently involved in a study to determine the indicators of quality health care for persons with Parkinson's disease. Using a literature review, followed by input from expert Parkinson's clinicians, a series of indicators were established, published, and distributed

throughout the VA health care system. Numerous bench research projects, clinical trials, clinical demonstrations and rehabilitation projects are also underway at the individual PADRECCs.

RR&D has recently funded several studies on rehabilitative strategies for Parkinson's disease. RR&D investigators are working to develop a valid method for measuring and interpreting the energy costs of activities of daily living for persons with physical impairments, including Parkinson's disease. They are utilizing body weight supported treadmill training to research re-teaching the body the proper gait patterns following trauma and during disease processes that compromise the ability to walk. They are also evaluating neurobiological and postural control mechanisms underlying the risk of falling in elderly veterans. In addition, RR&D investigators are studying the application of magnetic energy (accelerated Transcranial Magnetic Stimulation) to lessen depression and alleviate motor symptoms of Parkinson's disease.

Diabetes

Diabetes is one of the leading causes of disability and death in the U.S. Approximately 18 million people have diabetes mellitus, and each year over one million more people over the age of 20 develop the disease. By the year 2025, it is predicted that nearly 10% of our population will have diabetes.

VA is the largest integrated healthcare system in the U.S. providing care to people with diabetes. One in six veterans have this disease, and veterans with diabetes account for nearly 25% of all VA pharmacy costs and for more than 1.7 million hospital bed days of care annually. Diabetes affects nearly 20% of veterans receiving care in the VA healthcare system and is a leading cause of microvascular complications, such as blindness, end stage renal disease, and amputation. Moreover, middle-aged persons with diabetes have two to four times the risk of coronary artery disease and stroke compared to similar persons without diabetes.

All four Research Services of the Office of Research and Development have made funding for diabetes research a high priority. Over the past five years, VA funding for diabetes research has increased to over $16.8 million in FY 2004. Since FY 1999, non-VA funding has grown by more than $13 million with VA investigators now

leveraging over $35.8 million in non-VA funds in FY 2003. Some of the areas of research include:

- diabetes-related complications in aging and effects of exercise and diet,
- regulation of glucose transporters and gene transcription by insulin and glucose,
- pathogenesis and genetics of diabetic neuropathy and diabetic retinopathy,
- molecular mechanism of insulin resistance,
- linkage analysis and genetic studies of type-2 diabetes,
- islet transplantation studies, and
- rehabilitative strategies for Diabetes.

CSP is currently conducting a large-scale trial to determine if intensified blood-sugar control and management reduces major vascular complications that lead to most deaths, illnesses and treatment costs for type-2 diabetic patients. Patients will receive either standard diabetic drug therapy or an enhanced, additive therapy regimen designed to maintain tight control over blood sugar levels. Patient accrual for this study was completed in May 2003, with 1792 patients from 20 VA sites being randomized for participation. This study began in May 2000 and has a targeted completion date in 2008, after a 5-year patient follow-up.

We have seen great improvements in the quality of care and health outcomes of veterans with diabetes as a result of the HSR&D Diabetes Mellitus Quality Enhancement Research Initiative (QuERI) in Ann Arbor, MI. The Diabetes Mellitus QuERI is part of a VHA-wide effort to improve the quality of patient care in ways that are measurable, rapid and sustainable. It is charged with identifying and evaluating diabetes care practices, current gaps in care, and interventions to improve care and patient outcomes for veterans with diabetes. The Diabetes QuERI has several objectives and is concentrating on a number of areas highlighted within the VHA/DOD clinical practice guidelines, including glycemic control, hyperlipidemia, hypertension, and screening and early intervention for retinopathy and foot complications. The Diabetes QuERI can facilitate the implementation of interventions and care processes that are most likely to produce substantial improvements in the quality and length of life

for many veterans with diabetes as well as promote the most efficient use of VA resources.

Recent accomplishments of the Diabetes Mellitus QuERI in clinician and patient education, as well as clinical practice support tools include:

- development of educational briefs on glycemic, blood pressure and lipid control,
- development of a brochure that translates the *National VHA Diabetes Clinical Guidelines* into lay language for distribution to veterans with type-2 diabetes,
- creation of personalized diabetes profile worksheets that use the patients own test results to assist them in understanding the recommendations in the *National VHA Diabetes Clinical Guidelines* and to facilitate goal setting,
- participation in registry development for diabetes patients with high risk feet, and
- development of a patient survey instrument and organizational assessment tool for diabetes patients at high risk for amputation.

HSR&D has recently funded several other studies with significant impacts. Investigators have shown that VA facilities with higher levels of programming coordination and feedback coordination have significantly lower foot amputation rates. They have also demonstrated that improved blood pressure control in patients with type-2 diabetes leads to substantially reduced risks of cardiovascular events and mortality. Additionally, they have shown that physicians' communication and participatory decision-making style were both strongly associated with patients' reported diabetes self-management.

In BLR&D and CSR&D, several studies are underway examining the causes, pathogenesis and treatment of Diabetes. VA researchers have just completed the largest prospective epidemiological study to date comparing auditory function in diabetic and non-diabetic veterans. Preliminary results indicate that significantly poorer hearing exists in diabetic veterans compared to non-diabetic veterans 60 years of age or younger, but no significant difference exists in the two groups over 60 years old. These results may bring about changes in the standard of care provided to diabetic patients, including routine hearing tests to reveal changes in hearing status. Other investigators

are exploring the effects of physical activity, body weight and genetics on Diabetes aimed ultimately at improving treatments for veterans with Diabetes.

Investigators in RR&D are researching rehabilitative strategies for diabetic patients. They are involved in the developmental testing and enhancement of VA Pedorthic Computer-aided Design and Computer-aided Manufacturing (CAD/CAM) of orthopedic footwear to alleviate painful and debilitating conditions of the feet associated with diabetes. They are also evaluating the efficacy of a telerehabilitation system designed to improve post-discharge care to veterans who have had a recent lower limb amputation or who have a leg or foot ulcer. In addition, RR&D researchers are examining how somatic sensory dysfunction contributes to slips and falls in an older, diabetic population.

Alzheimer's Disease

Alzheimer's disease is a complex illness that causes the gradual loss of brain cells. Although the disease was once considered rare, research has now shown that it is the leading cause of dementia. Approximately 4.5 million Americans have this disease, and it is a major cause of morbidity and mortality among veterans. Although many things about Alzheimer's remain a mystery, research continues to bring us a better understanding of the disease, more accurate diagnoses, and more effective treatments.

VA supports a broad array of studies related to Alzheimer's disease. Over the past five years, VA funding for Alzheimer's disease research has increased to over $6.3 million in FY 2004. Since FY 1999, non-VA funding has increased by over $12 million to nearly $42.8 million in FY 2003. Some of the areas of research include:

- vaccine development for Alzheimer's disease,
- advances in neuroimaging technologies to monitor disease progression,
- gene therapy in animal models,
- mechanisms of damage to nerve cells,
- inflammatory mechanisms in Alzheimer's disease,
- gene–Environment interactions in Alzheimer's disease, and
- therapeutic interventions.

Investigators in BLR&D and CSR&D are working on developing non-invasive techniques that would allow early identification of patients with Alzheimer's disease prior to the onset of severe memory loss or other cognitive deficits. Investigators are also working with imaging technologies to discover ways to easily monitor the disease progression and response to therapy. Other VA researchers are involved in a project to develop an Alzheimer's disease vaccine and are examining the potential of other pharmaceutical interventions.

HSR&D has also recently funded several significant studies on the quality of care and outcomes of veterans with Alzheimer's disease. Investigators demonstrated that veterans with dementia who receive appropriate interventions from caregivers might be able to remain at home longer in environments that promote maximum independence for both caregivers and patients.

HSR&D researchers have also revealed a significant relationship between discomfort and agitation among nursing home residents with dementia, suggesting that agitated behaviors may be associated with increased pain. Accordingly, better quality of life for long-term care residents may result from regularly scheduled pain management. In addition, researchers are working to help provide an environmentally safe home living situation for veterans with dementia by giving caregivers the know-how and self-confidence to prevent risky behavior that leads to injuries.

Among other studies, RR&D is working in partnership with the Rosalynn Carter Institute (RCI) for Human Development on two exciting initiatives. RR&D is a member of the National Quality Caregiving Coalition (NQCC), a group sponsored by RCI. RCI, in collaboration with RR&D and other interested groups, is developing a national report card on care giving in America. Work on the report card is in its initial planning stages to define the pertinent variables to be included and questions to be asked. RR&D will be involved in all stages of this project. RR&D is also taking the lead in planning a joint research project between the Atlanta VAMC and RCI to examine a caregiver intervention program. This effort involves RR&D central office research staff, central office clinical care staff, VAMC Atlanta clinician scientists and RCI staff.

Four exciting projects examining new potential treatments for Alzheimer's disease will be reviewed this June for funding in FY 2005. Two of these projects examine the effectiveness of ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDS) to preserve cognitive function and prevent the pathological damage. The third project examines the efficacy of an herbal supplement component reported to be a memory enhancer and natural therapy for Alzheimer's disease. The last project examines two potential Alzheimer Disease therapies: immunization/vaccine development and cholesterol lowering drugs (statins).

We are very proud of VA's accomplishments in Parkinson's disease, Diabetes and Alzheimer's disease research, and we remain committed to maintaining the highest quality research in the country to best serve the needs our nation's veterans.

Mr. Chairman, this concludes my statement. I will now be happy to answer any questions that you and other members of the Subcommittee might have.

Statement of
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Associate Chief of Staff for Research and
Director, Diabetes Health Center
Hunter Holmes McGuire VA Medical Center, Richmond, Virginia
Before the
Subcommittee on Oversight and Investigations
Committee on Veterans' Affairs
House of Representatives
April 28, 2004
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Mr. Chairman and Members of the Subcommittee:

I speak to you today in a dual role. For 27 years I have been Associate Chief of Staff (ACOS) for Research at McGuire VA Medical Center in Richmond. I am also Director of the Diabetes Health Center at McGuire, which is one of VA's two designated Centers of Excellence in Diabetes. I am going to confine my remarks to how ongoing research intersects with the day-to-day care of patients in the Diabetes Health Center, which is our main concern.

Ten years ago, 14% of the veterans who received outpatient prescription medications at McGuire received medications for diabetes; today it is 24%, and next year it will be more. To give you some idea of the economic impact, this 24% of our patients is responsible for 44% of our total outpatient expenditures for drugs. (The 44% figure includes both diabetes medications and medications for other conditions.) As our population ages and the rate of obesity continues to rise, the economic impact of diabetes will continue to grow. Well over half the heart attacks in this country occur in people who have either diabetes or its precursor, which is known as "insulin resistance syndrome" or "metabolic syndrome." Most heart attacks among type 2 diabetics, like the other complications of diabetes, should be preventable. However, because there are so many type 2 diabetics, prevention becomes challenging.

The main reason I have practiced in the VA for 30 years is that I feel VA is a particularly favorable place for giving good diabetes care. Among our advantages are the computerized patient record; the fact that we keep our patients for many years; and the veterans themselves, who are a particularly rewarding group to deal with and who,

in my opinion, participate in their care more diligently than the average private sector patient population.

I'd like to address how research fits into our busy clinical operation. I will limit my remarks exclusively to what we are doing in Richmond; many other VA medical centers have analogous stories. The VA research program covers a wide spectrum of studies, from basic physiology to clinical studies to new structures of care delivery, and all these studies are patient-focused. The most basic VA projects grow out of what we see clinically every day. For example, the fundamental driver of the increased prevalence of diabetes is our society's epidemic of obesity. My colleague, Dr. James Levy, runs our weight management program at McGuire, and his primary concern is preventing people from regaining the weight they have lost. This has led him to study the regulation of secretion and action of leptin, the hormone from fat cells that is an important regulator both of appetite and of energy expenditure. His studies in rodents have already produced some unexpected findings; for example, rats greatly increase their energy expenditure when they are fed omega-3 fatty acids (from fish oil). I doubt that many of us would ever think of feeding fish oil to rats; the idea came from a few patients with metabolic syndrome who were treated with fish oil for their high plasma triglycerides and whose fatty livers unexpectedly improved. This is an example of basic research flowing directly from clinical care.

Turning to clinical research, there are many therapeutic studies on all aspects of diabetes. To take just one example, the VA Diabetes Trial is a cooperative study at 20 VA medical centers testing whether extremely tight blood sugar control reduces the incidence of heart attacks and strokes in type 2 diabetics. In terms of how people are actually treated, this may be the most important unanswered question in diabetes today. The biggest medical problem confronting the older type 2 diabetic is coronary heart disease, and our studies so far do not clearly show whether maintaining a normal glucose reduces the incidence of that disease – or, indeed, whether it actually makes it worse. Without clear data, we might devote massive effort and resources to normalizing everyone's glucose only to find in 10 or 20 years that we had been doing exactly the wrong thing. The VA Diabetes Trial will address this question and attempt

to answer it. The 63 veterans at Richmond who are participating in this trial will, thus, make a contribution toward establishing an international standard of care.

Current VA research is also addressing therapies that we know are effective, but that are also difficult to apply in clinical practice. For example, I mentioned that well over half the heart attacks in this country happen to people who have either the metabolic syndrome or diabetes. The majority of these could be prevented if all the therapies we know to be effective were instituted to their maximum effect – lifestyle modifications, cholesterol and triglyceride lowering, blood pressure control, aspirin, beta blockers, ACE inhibitors, etc. The problem is how to apply these effective therapies to the large number of patients who would benefit from them. Our current research in care delivery at Richmond involves a pilot Metabolic Syndrome Clinic, in which a group of veterans with high heart attack risk has six visits at monthly intervals during which we identify and manage multiple cardiac risk factors simultaneously. Five hundred veterans have completed the full sequence of visits. One of our patients referred to this program as "metabolic syndrome boot camp," but all of us have been impressed with its effectiveness. Over 70% of the patients have achieved their very stringent lipid and blood pressure goals. Everything we do in this clinic has long been known to reduce coronary risk, but in the country as a whole most people with high coronary risk do not fully benefit from these effective therapies because of the difficulty in delivering them to the large numbers involved. This is one of many areas in which VA functions as a laboratory for finding the best ways of delivering therapies which we know work.

Mr. Chairman and Members of the Subcommittee, I have tried to give a few examples of the spectrum of diabetes research in Richmond and to show you how it all flows directly from or to VA medical care, which is our primary focus. I will be happy to answer any of your questions. Thank you.

Statement of
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Edith Nourse Rogers VA Medical Center
Bedford, Massachusetts
Before the
Subcommittee on Oversight and Investigations
of the
Committee on Veterans' Affairs
United States House of Representatives

April 28, 2004
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Mr. Chairman and Members of the Subcommittee:

I'm pleased to appear before the Committee to discuss Parkinson's disease research within the VA and as it pertains to the Edith Nourse Rogers VA Medical Center. For the past 36 years I have conducted studies on the effects of disease on brain function, of which 22 years were at the Massachusetts General Hospital and Harvard Medical School, with the past 14 years directing a research program in developing therapies for brain diseases in the Geriatric Research Education and Clinical Care Unit.

The broad goals of the VA health care system remain constant in the mission to treat, cure, and if possible to prevent disease, while providing the best possible health care to veterans. As part of this mission, VA has developed a well-regarded medical and scientific research program.

Brain diseases have a devastating impact upon veterans. As the veterans population ages, the incidence of these neurological conditions will substantially increase. VA has made a serious commitment to improving patient care and identifying a cure for brain diseases, particularly Parkinson's disease.

Parkinson's Disease (PD) is the second most common neurodegenerative disorder, affecting more than 500,000 Americans. It is projected to surpass cancer as the second most common cause of death among the elderly by 2040. PD results from the loss of specific neurons in the midbrain, causing tremors, slow movement, stiffness, and gait problems. The disease is highly debilitating, interfering with employment and normal activities of daily living. There are

approximately 60,000 new cases diagnosed each year. VA medical centers treat at least 40,000 PD patients each year. Despite many advances in therapy, no drug treatment appears to slow or prevent disease progression.

While the specific cause of PD is unknown, a number of hypothetical causes have been suggested, with evidence for a role of both environmental and genetic causes. Studies have suggested that PD is associated with occupational exposure to pesticides and industrial chemicals. Studies identifying genetic factors contributing to the disease have led to the identification of genetic mutations in PD.

VA has played a significant role in the current understanding of PD, as evidenced by the large publication record of VA clinical and scientific investigators. VA research has helped to describe the fundamental clinical, pathological, and molecular features of PD and related disorders. VA is at the forefront in developing a therapy for PD. In 1999, VA and the National Parkinson's Disease Foundation established an alliance dedicated to finding a cure for the disease, confirming VA's substantial commitment to understanding, treating and curing Parkinson's disease.

In 2001, VA announced an innovative healthcare delivery model for veterans with PD by opening six new Parkinson's Disease Research, Education and Clinical Centers (PADRECCs), specializing in Parkinson's disease research, education, and clinical care. Each PADRECC is involved in basic biomedical research, rehabilitation, health services delivery, and specialized clinical trials.

In 2003, VA developed a national consortium network for dispersed VA clinicians to resource the VA's expertise in PD through the PADRECCs. The consortium is now comprised of 150 multidisciplinary clinicians. This National VA Parkinson's Disease Consortium will serve as a mechanism for collaboration, facilitate intellectual exchange, endorse patient advocacy by developing educational programs, enhance clinical training in PD, support the delivery of telemedicine services, and promote scientific research.

I direct a research program at the Bedford VAMC developing therapies for neurodegenerative disorders that are particularly focused upon finding a

treatment for PD, Lou Gehrig's disease (amyotrophic lateral sclerosis, or ALS), and Huntington's disease. We use scientific models of PD to test the effects of drug compounds to prevent the cell loss that may result in clinical and pathological aspects of PD. Once these drugs are found to work in the neurological models, human clinical trails are begun through the VA clinical trials program. We have a number of very promising therapies to slow the progress of PD and other like brain disorders, such as ALS.

VA is an excellent and productive training ground for future investigators in PD. The influence of VA extends well beyond its boundaries. The success of the VA research program in PD is based upon strong institutional commitments by the medical service and a cohesive community of scientists and clinical investigators and their broad experience in neurological diseases. VA will build upon their past accomplishments and will continue to conduct research that will ultimately help in the search for a cure for PD. VA is positioned and ready to meet this challenge.

That concludes my statement. I would be happy to answer any of your questions. Thank you.

Statement of
Dr. Mary Sano
Associate Chief of Staff for Research
VA Medical Center, Bronx, NY
Before the
Subcommittee on Oversight and Investigations
Committee on Veterans' Affairs
U.S. House of Representatives

April 28, 2004

Mr. Chairman and Members of the Subcommittee:

Though new to VA, I have been a researcher in Alzheimer's disease (AD) for nearly 20 years, with a primary interest in developing strategies for the treatment and prevention of the disease. Currently, I am directing a multi-center clinical trial to determine if lipid-lowering drugs slow the progression of AD. This is run with a consortium of Alzheimer's Centers around the country, and includes several other VA sites.

One of the first observations to support the idea that the use of cholesterol lowering drugs could have benefits in this population was made by Dr. Benjamin Wolazin, a physician at the Edward Hines VA Medical Center (VAMC) in Hines Illinois. Through record review, he determined that the prescriptive use of certain drugs known as "statins" was associated with lower risk of AD. While observational studies only give a hint about potential benefits, we are now conducting a rigorous randomized trial that is designed to determine if one of these agents will slow disease progressing in patients with mild to moderate AD.

The Alzheimer's Disease Research Center, located at the Bronx VAMC and at Mount Sinai School of Medicine in New York City, which I direct, provides an infrastructure to use state of the art clinical assessment of patients and to offer patients the opportunity to participate in cutting edge research. One of the most valuable resources at our medical center is the brain bank for AD and other cognitive disorders. This resource permits us to conduct clinical-neuropathological correlations to determine the changes that occur in the brain with aging and disease. Because of the careful clinical diagnosis with electronic

record keeping at VAMCs, we are able to maximize the very generous contribution of our volunteers to compare detailed information from their medical records with subtle and microscopic changes at the cellular level to get a clearer picture of the biology of AD. This resource has led to an important observation about cell loss. We know that AD is associated with neurofibrillary plaques and tangles. From these studies we can surmise the areas of the brain that appear to deteriorate first. For example, the areas known as the entorhinal cortex and the hippocampus appear to deteriorate first. These brain areas are involved with memory and learning, and we now know that serious impairments in memory may predict AD several years before the disease can be diagnosed. We also know there is definite loss of neurons in AD, but in healthy eldery individuals and in very mild cases, there are apparently normal neurons that undergo the initial stages of tangle formation. Furthermore, the loss of neurons is limited, compared to AD cases. This is important because it suggests that we may be able to "rescue" neurons at this mild stage and therefore we may focus our attention to treatments at this early stage.

VA has a long history of research in AD. The very first multi-center study for an approved treatment for AD was published in the New England Journal of Medicine under the leadership of a VA physician, Dr. Kenneth Davis, the former Chief of Psychiatry at the Bronx VAMC. This work made a long-standing contribution in that it provided the methodology for conducting multi-center studies for testing new treatments for AD. That methodology is still used today. In particular, the very test used to determine drug efficacy in dementia in nearly all pivotal studies is the Alzheimer's Disease Assessment Scale (ADAS), which was developed at the Bronx VAMC. Though this test was published nearly two decades ago, it remains the most commonly used assessment in clinical trials for AD in the U.S. and around the world.

Many renowned VA AD research colleagues, who have been in the field for years, have made important contributions. From "bench to bedside" is the challenge for VA research, and it is met in the research of Mark Tuszynski, MD, PhD, (San Diego VA Medical Center), through his pioneering work examining

fibroblasts and, more recently, other types of cells. These cells have been transduced to express genes for growth factors such as nerve growth factor (NGF), and then transplanted into the brain. This work started about a decade ago with funding from VA and has proceeded to show that grafts could reverse memory deficits resulting from lesions associated with AD pathology. This work subsequently advanced to studies in monkeys, and, two years ago, to the first clinical trial of gene therapy in patients with AD, who are transplanted with their own fibroblasts, which have been transduced to produce NGF. Much of the preliminary work is attributed to the published work of Dr. Tuszynski, and this interventional approach provides great hope for effective treatment.

While finding cures and preventions are important, even our best efforts will leave many with AD. VA researchers have done cutting edge research to define and maximize patient independence and comfort. To that end, VA researchers have described the standards of determining "decision making" capacity in patients with AD. The rigorous research conducted lays the foundation for determining the best way to evaluate patient ability to participate in clinical and research decisions.

A report of the National Ethics Committee of the Veterans Health Administration (lead author: Dr. Ladislav Volicer, Edith Nourse Rogers Memorial VAMC, Bedford Massachusetts) summarizes the empirical data on the important role of families in making decisions for patients with impaired capacity. The report found that even when asked prior to the onset of any limitations due to illness, patients prefer that a family member make decisions for them, and often prefer this to advanced directives. Therefore, an important conclusion from this report is that we need to make decisions that truly meet patients' needs and desires. The report also contains specific recommendations for the advance proxy planning process.

In summary, the success of AD research in VA is the result of a series of partnerships. These partnerships begin with the generous spirit of the veterans who volunteer to participate in VA clinical research. They include the melding of clinical resources, such as the electronic medical record system and centralized

databases, with the outstanding curiosity of VA researchers, and would not be possible without the research resources to make the best use of the scientific opportunity and the commitment to deliver the best of care.

Diabetes Research and Wellness Foundation
1206 Potomac St. NW
Washington, DC 20007

Chairman Steve Buyer

Dear Chairman Buyer,

Attached please find the statement for the record on diabetes. The Diabetes Research and Wellness Foundation strongly believes in its mission of keeping those with diabetes healthy until a cure is found.

I have provided this committee with an overview of diabetes and the impact this disease has on those afflicted with diabetes. I am hopeful that by raising the awareness of the seriousness of this disease, funds and resources may be allocated to improve the life of these patients. Managing diabetes is a full time job, and my patients valiantly attempt to control their disease. Through efforts of this committee it is my hope we all can work toward prevention and maybe even a cure for this devastating disease.

Respectfully,

Kathleen A. Gold, RN, MSN, CDE

Kathleen A. Gold RN, MSN, CDE

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Introduction
Mrs. Gold is an active leader in the battle to take Diabetes Education to every diabetic. As a Certified Diabetes Educator she is a member of the Medical Advisory Board and the Diabetes Education Specialist for the Diabetes Research and Wellness Foundation. Mrs. Gold is the editor of the Diabetes Wellness News, operates a national diabetes help line and provides a Diabetes Clinic for the Unity Health Care Clinic at the Federal City Homeless Shelter in Washington, DC and a Spanish clinic at Upper Cardoza Health Care Clinic. Mrs. Gold is the past president the National Capital Area American Association of Diabetes Educators; she serves on Virginia Diabetes Council Patient Issues Committee and the University of the District of Columbia Extension Program Advisory Board.

Diabetes Research and Wellness Foundation **1997-present**
Member Medical Advisory Board; Diabetes Help Line; Newsletter Editor, and Staff Writer. *Activities include:* Community screening and education programs, Continuing education program, Community Preceptor George Washington University/George Mason University Iscopes Project, weekly diabetes class at the Upper Cardoza Unity Health Care Clinic, Diabetes Clinic for the Unity Health Care Clinic at the Federal City Homeless Shelter in Washington, DC.

INOVA Home Health Agency **1993-1997**
Home care nurse and preformed diabetes education.

St. Agnes Hospital **1975-1983**
Nursing Administrator, Clinical Head Nurse for the Medical ICU

National Institutes of Health, Open Heart **1974-1975**
Staff Nurse

Education
Masters of Nursing 1974
University of Maryland School of Nursing, Baltimore, MD

Bachelors of Science, Nursing 1972
D'Youville College, Buffalo, NY

Statement for Hearing on Veteran's Administration Research on Diabetes

Diabetes is a group of metabolic diseases that results in a high level of blood glucose due to either a low production of insulin or a defect in the action of insulin. Insulin is a hormone produced by the pancreas, an organ located in the left side of your lower abdomen. The pancreas, which is about the size of a banana, contains beta cells which are responsible for the production of the hormone insulin. Approximately 5-10% of the cells within the pancreas are beta cells. Insulin is required for the proper utilization of glucose's conversion to energy in the cell. It can be likened to the gas that fuels an automobile. Glucose is the fuel source for cells; however for glucose to be transported into the cell, insulin must be the delivering agent.

There are three primary types of diabetes. Type 1 diabetes is an autoimmune disease, which destroys the insulin producing beta cells in the pancreas. Type 1 diabetes usually occurs in children and young adults however it may occur at any age. Type 1 accounts for approximately 10% of diabetes cases. Research continues to determine those at risk and what interventions may be instituted to reduce their risk. Research is being conducted to reverse or prevent the progression to diabetes.

Type 2 diabetes is more common, as approximately 90% of individuals with diabetes have type 2. Type 2 diabetes is a condition of insulin resistance. Individuals with type 2 diabetes produce defective insulin in large quantities in an attempt to move glucose from the blood into the cells. However, because their insulin is not functioning properly, the body reaches a point in which it can no longer meet its demands. As a result, type 2 diabetes manifests itself. Type 2 diabetes is closely correlated to obesity. As we see the rates of obesity increase nationally, type 2 diabetes is following close behind.

Risk factors for type 2 diabetes include: age, obesity, family history, history of diabetes during pregnancy, polycystic ovarian disease, hypertension, elevated blood cholesterol, and a sedentary lifestyle. It is also found in higher proportions in certain ethnic groups: African Americans, Hispanics and Latinos, Native Americans, Pacific Islanders, and Asian Americans. In recent years we have also seen an increased incidence of type 2 diabetes in children and adolescents that is directly linked to obesity and lack of physical exercise.

The third type of diabetes occurs during pregnancy and is called gestational diabetes. As hormone levels change during pregnancy, insulin resistance may develop resulting in elevated blood glucose levels. To avoid complications to the unborn child it is important to maintain normal blood glucose levels during the pregnancy. Following pregnancy, it is often found that about 5 -10% of those diagnosed with gestational diabetes have type 2 diabetes. Women who have had gestational diabetes have a risk of 20 – 50% for developing type 2 diabetes later on in life.

Other causes of diabetes can be related to removal of the pancreas, certain medications, infection, other illnesses and MODY (maturity onset diabetes of youth), a genetic disorder in which insulin production stops, are all examples of events that can lead to the development of diabetes.

Signs and Symptoms

The signs and symptoms of diabetes are: extreme thirst, frequent urination, blurred vision, dry skin, extreme fatigue, non-healing wounds, and weight loss. In individuals with type 1 diabetes, these symptoms appear rapidly. An individual may be so ill that hospitalization may be required. In contrast, individuals with type 2 diabetes may have high blood glucose levels for long periods of time and the onset of symptoms is much more insidious.

High levels of blood glucose cause the filtering system of the kidneys to remove the glucose from the blood resulting in a loss of large amounts of water in the urine. This in turn causes an increased thirst. Vision is affected as a result of the impact on elevated glucose levels on the very small blood vessels of the eye. Once blood glucose levels are stabilized the blurred vision resolves. Wounds have a difficulty healing due to the inability for white blood cells and other nutrients to reach the damaged tissue due to the quantity of blood glucose in the system. And lastly weight loss and fatigue occur because insufficient amounts of insulin prevent the cells from absorbing glucose resulting in starvation of the cells causing extreme fatigue. In response the body then breaks down fat as the energy source resulting in rapid weight loss.

For those individuals experiencing weight loss due to lack of insulin production treatment with insulin injections will reverse this process. Individuals with type 1 diabetes, therefore, require daily injections of insulin to ensure survival.

Individuals with type 2 diabetes have a slow onset of symptoms and may not be aware of any abnormality. Frequently, type 2 diabetes is recognized because an individual complains of symptoms from one of the complications of diabetes. This includes neuropathy, heart disease, non-healing wounds, and diabetic retinopathy – damage to the small vessels of the eye which left untreated can result in blindness.

Prevalence

In the United States, 18.2 million (6.3%) of the population has diabetes. Of these, 13 million are diagnosed and 5.2 million are undiagnosed. These numbers are growing at an alarming rate. Currently, 8.7% of the population over the age of 20 has diabetes, and the percentages increase with age. Individuals over the age of 60 have an 18.3% rate of diabetes. Race and ethnicity are significant factors to developing diabetes, 11.4% of African-American population, and 8.2% of Hispanic/Latino-

American population (Mexican Americans are twice as likely to develop type 2 diabetes) have diabetes. Native Americans and Alaskan Natives have a 14.9% risk and a tribe of Native Americans in the Southwest have an incidence of 27.8%. Asian-Americans and Native Hawaiians as well as other Pacific Islanders are twice as likely to develop diabetes as whites living in Hawaii.

With the increase of obesity among children, the incidences of type 2 diabetes in children have risen dramatically within the past 10 years. Programs for good nutrition, improvement in school lunch programs and physical education in the schools are needed to teach and implement healthy lifestyles among this age group. Families must also assume responsibility and provide a nutritious, well-balanced diet as well as encourage physical activity for their children.

Diagnosis

The criterion for diagnosis is a fasting blood glucose level above 126 mg/dl or a blood glucose level above 200 mg/dl 2 hours after eating. Due to the high number of individuals that are diagnosed with complications, identifying those at risk at an earlier point of the disease is necessary. Recent research in preventing the onset of Type 2 diabetes has resulted in the classification of prediabetes. The diagnosis of prediabetes is blood glucose measurements of 100-125 mg/dl after an 8 hour fast or a 2 hour post meal blood glucose level of 140-199 mg/dl. It is hoped that identifying these at-risk individuals at earlier stages, lifestyle changes may actually prevent or at least delay the onset of type 2 diabetes.

Prediabetes

In the Type 2 Diabetes Prevention Program (DPP), a cross section of individuals from 40 – 74 with impaired glucose tolerance were studied. These individuals were placed in one of three groups. One group was given intense lifestyle interventions. They were provided with education and counseling to lose 5-7% of their body weight through the reduction of fat calories and the addition of 30 minutes of walking per day. Group two was prescribed a medication – glucophage. Finally, group three was the control group received a placebo in place of glucophage, group two and three also were provided basic information on diet and exercise. The trial found that 58% of those who lost weight and exercised daily did not develop type two diabetes, while those taking glucophage only 31% were protected in comparison to those in the control group.

Treatment

Treatment consists of life style changes that include exercise, proper food choices, monitoring and medication. Education is the core treatment for individuals with type 2 diabetes. Individuals must

make lifestyle and behavioral changes in order to manage their diabetes. This is a difficult task. Many individuals with diabetes are given pills, instructed to lose weight and exercise with no further support. One wonders why changes do not happen. Understanding the impact of food, primarily carbohydrates on blood glucose control, is vital to good management.

Monitoring

Having the capability to monitor blood glucose levels permits patients to act on those results and adjust behavior and/or medications. Monitoring is expensive and is covered by Medicare and many health insurance plans. Reimbursement places restrictions on the number of strips a patient is allowed to monitor their blood glucose per month. However, not all individuals with diabetes have insurance or are enrolled in plans that provide this benefit. Frequently individuals with type 2 diabetes are not prescribed a meter which makes it very difficult to self-manage their disease.

Meal planning

Food choices are significant in the management of blood glucose levels. Individuals with diabetes must learn to read and understand labels on food products. They must learn to assess portion sizes of foods, and they must determine through trial and error the effect of foods on their blood glucose levels. A balanced, healthy diet is needed to control diabetes and this takes time and effort. Individuals with diabetes are not on a diet but must make life long changes in their eating habits.

Timing of meals is another consideration, since most individuals are on medication, it is important that they eat at specific times in order to obtain the optimum benefit from their medication regimen. A frequent misstatement is that individuals with diabetes may not eat sugar. Sugar does not elevate blood glucose levels any higher than a piece of bread or a potato. Therefore, in any meal plan sugar is allowed, in moderation. To understand meal planning and the effect of foods on blood glucose control, individuals should be encouraged to consult with a Registered Dietitian to receive detailed education regarding their individualized meal plan needs. There is no such thing as a diabetic diet but rather a plan is developed considering an individual's likes and dislikes. It is important when asking someone to make major behavior changes that education, support and consideration of what is truly realistic be considered.

Exercise

Exercise is significant in the control of blood glucose levels. Walking for 30 minutes may effectively lower blood glucose levels of a person with diabetes as much as 60-100 points, depending on the intensity. Exercise is a key treatment for diabetes. In individuals with type 2 diabetes not only is

exercise important for blood glucose control but it is also necessary for weight loss. If food choice and exercise are not effective in lowering blood glucose levels it may be necessary to add medications.

Medication

For those with type 1 diabetes multiple insulin injections daily or the use of an insulin pump are required for survival. There are three primary defects in the metabolic pathways of individuals with type 2 diabetes. First, due to the long time overproduction of insulin the pancreas can no longer maintain insulin production at the levels required to lower blood glucose levels, second, the liver which stores glucose and releases it on an as needed basis tends to continually leak glucose into an already saturated system, and lastly the insulin produced by individuals is defective and unable to open the door and transport glucose into the cell. In order to treat these defects multiple medications may be required as well as insulin.

In recent years our medication treatment options have increased dramatically. There are a variety of insulins now available that work in as little as 15 minutes, lasting for 2- 3 hours. A new insulin that acts as basal or background insulin lasts for 24 hours. There are also many new oral medications that stimulate the pancreas to produce more insulin, medications that restrict the liver's release of stored glucose into the body, medications that limit the body's ability to absorb carbohydrate, and medications that target the issue of insulin resistance are all helping control the blood glucose levels. It is not uncommon for individuals with diabetes to now take two or three oral medications as well as insulin injections in order to achieve balanced control.

A report by the CDC Diabetes Control Program shows the breakdown of medication regimens used by patients from 1999 -2001. Fifty-three percent were treated with only oral medication, 19% received only insulin, 12% received insulin and oral medication, and 15% received neither oral medication nor insulin. As a result individuals with diabetes are generally on complex and costly medication regimens. Not only do they require medication to treat their diabetes, but other co-morbid conditions may exist as well.

The UK Prospective Diabetes Study (UKPDS) revealed that to reduce the risk of complications in individuals with diabetes it was necessary to maintain a normal cholesterol level and a normal blood pressure as well as blood glucose levels. Therefore, since type 2 diabetes, hypertension and dyslipidemia are frequently linked these individuals may be required to take a large number of medications on a daily basis.

The Diabetes Control and Complications Trial (DCCT) and the UKPDS diabetes study found that individuals could actually impact outcomes by keeping blood glucose levels in good control. However, the cost to the patient in time and money is significant.

As the course of diabetes progresses, it is not uncommon for the addition of insulin to become necessary for individuals with type 2 diabetes. However, in today's world the addition of insulin to a treatment regimen is considered a failure by patients. Physicians frequently use the threat of insulin as an attempt to encourage patients to make necessary lifestyle changes. Insulin should not be viewed as an arrival of doom but rather another addition to the armament of therapy required keeping an individual healthy. Insulin should be viewed as the natural progression that allows for better control of blood glucose levels. With the new insulins available as well as the availability of insulin pump therapy, patients have the tools needed to manage their diabetes effectively. However, to do this they must have an excellent understanding of their disease and the impact of food, exercise and medications. This is a full time job from which there are no vacations.

Insulin pump therapy

Insulin pump therapy is another option being used by many patients with type 1 diabetes. It is primarily used in those with type 1 because insurance in most cases will only cover this technology if an individual has type 1 diabetes. The use of the insulin pump mimics what the body does naturally by providing a continuous infusion of insulin (basal insulin rate).Based on blood glucose levels and food intake individuals calculate the amount of insulin required at meal time (bolus insulin rate). Insulin pump therapy allows for very low doses of insulin to be administered, greater flexibility in eating and exercise and is much more accommodating to today's busy lifestyle. Pumps are being used more frequently with children and adolescents to improve control with minimum risk of hypoglycemia (low blood glucose reactions).

Diabetes Self-Management Training

Diabetes is a disease in which the patient should be given the information needed so they may have an understanding of their disease and the best means of managing it. Although there is no cure for diabetes it may be managed and controlled. However, that management requires a fair amount of effort by the patient and their healthcare provider. These are complex patients to manage and motivate.

Many states have passed legislation, which allows for Diabetes Self-Management Training under specific guidelines. However there are many patients who are never referred to these services nor given the information required to manage their disease. The National Diabetes Education Program has made great strides in raising awareness of diabetes among minority populations and the public. However, the challenge of changing behaviors and providing the support required still looms as a major obstacle as diabetes reaches epidemic proportions.

Complications

Diabetes is the sixth leading cause of death; however this statistic may be deceivingly low due to the fact that diabetes may not be listed on the death certificate but rather heart disease, stroke, or kidney disease are listed as the cause. All of which are complications of diabetes. The risk of death among diabetics is approximately twice that of individuals without diabetes.

Heart disease is the leading cause of deaths among those with diabetes. The chance of having heart disease is two to four times higher in diabetics than those without diabetes. Research has demonstrated that elevated blood glucose levels cause an inflammatory reaction to the walls of blood vessels and over time this chronic inflammation affects the configuration of the blood vessel wall increasing the likelihood of plaque and fatty build up, resulting in a heart attack. Also longstanding diabetes affects the autonomic nervous system. Individuals with diabetes frequently lack the obvious symptoms of a heart attack and its occurrence may go undetected.

Hypertension frequently results in stroke and approximately 73% of adults with diabetes also have blood pressure readings above 130/80. Individuals with diabetes frequently require more than one type of medication to lower their blood pressure.

Kidney disease is a frequent complication of diabetes. Yearly evaluation of kidney function is necessary to identify those at risk for kidney disease and institute a preventive medication regimen of aggressively managing blood pressure and blood glucose levels. The use of blood pressure medications has been demonstrated as effective in slowing down the progression of kidney disease. Diabetes is the leading cause of end-stage kidney disease, accounting for 44% of all new cases. In 2001, 142,963 individuals with diabetes were on chronic dialysis or required a kidney transplant.

Blindness is frequently associated with kidney disease. Diabetes is the leading cause of new cases of blindness. Diabetic retinopathy, damage to the small blood vessels of the eye, results in approximately 18,000 new cases of blindness a year. Yearly eye exams are recommended once damage is detected. Patients frequently have these eye exams when first diagnosed however, as yearly check ups are normal they are not as attentive to follow-up at the point when they are more likely to develop the early stages of retinopathy.

Neuropathy occurs in approximately 60-70% of individuals diagnosed with diabetes and is frequently exists before the diagnosis of diabetes is made. Neuropathy is damage to the nervous system which is caused by a chemical imbalance at the nerve endings. This damage affects the transfer of information to the nerves causing impaired sensation or pain most commonly occurring in the long nerves of the hands and feet. However any nerve in the body may be affected by prolonged elevated blood glucose levels causing slowed digestion, constipation, erectile dysfunction, the heart's ability to adjust it rate, and is the leading cause of amputation.

Amputation is a result of nerve damage and impaired circulation caused by the effect of elevated blood glucose levels. A simple wound to the foot may result in an amputation if left untreated.

Individuals with diabetes are at increased risk of developing periodontal disease. Elevated blood glucose levels offer a medium for bacteria growth in the gums and teeth which can result to damage of the bones supporting the teeth. Good dental care is vital.

Struggles

Individuals with diabetes struggle daily with a multitude of issues, making correct food choices, following complicated medication regimens, testing blood glucose levels and acting on the results, fitting exercise into an already busy day. Individuals are taking numerous medications costing upwards of $500 a month, test strips cost approximately $.80 a piece and it is not uncommon to have to test 2-3 times a day. Those that are self-employed or working for small companies that do not offer insurance benefits are limited in their ability to care for their diabetes. Individual coverage may cost $900/month. For elderly patients on Medicare and on a limited income, although their strips and testing supplies are covered, the many expensive medications are not, leaving them to make a choice between taking their medication and paying their heating or food bill. Calls are received daily on our national diabetes helpline asking for some type of financial assistance or suggestions on how they may purchase affordable health insurance.

Job discrimination is another issue many individuals with diabetes must deal with on a daily basis. Timing of meals and snacks is vital to their self-management; however it is sometimes difficult to guarantee a lunch break at a specific time or the accommodations needed to test their blood glucose levels in the work place.

School issues are of constant concern for many parents of diabetic children. Legislation in many states is being passed to assure children the right to test their blood glucose levels in their classrooms and to accommodate their needs for testing, eating snacks and meals at a set time and educating school personnel on diabetes and its treatment.

In addition with the elimination of physical education programs and an unhealthy school lunch program the development of type 2 diabetes has increased dramatically. States now are looking at eliminating soda and junk vending machines from schools and re-evaluating a lunch program to assure students are receiving a healthy, nutritious diet.

Research

Significant research has occurred in the past 15 years to provide information regarding the reduction in complications of diabetes. The DCCT and the UKPDS demonstrated that controlling

blood glucose levels was significant in reducing the complications of diabetes. However a study done at NIH revealed that although we know that the lower hemoglobin A1C level reduces the risk of complications less than 12% of individuals with diabetes are meeting treatment goals for blood glucose, blood pressure and cholesterol. And in fact the number of those who have not met target levels actually increased by 7% over the past 10 years. Only 36% reached blood pressure goals of 130/80, and 52% have a total cholesterol level above 200. Although more individuals are on insulin therapy or oral medications only 37% have reached the recommended goal of less than 7. According to Dr. Judith Fradkin, director of NIDDK's Diabetes, Endocrinology, and Metabolic Disease Division patients are not following the recommendations made by their physicians to lose weight, reduce fat intake and exercise. Tools and incentive are needed to empower patients to take charge of their diabetes or the rate of complications will continue to rise.

The Diabetes Prevention Trial found that 58% of those individuals identified as being at risk of developing diabetes could actually prevent or delay that outcome with lifestyle changes resulting in weight loss of 5-7% by reducing fat calories and daily physical activity for 2 ½ hours a week. Research is continuing in this area to evaluate long term benefit of life style changes as well as an evaluation of the use of various medications used in the treatment of diabetes to assess their effectiveness of preventing or delaying the onset of type 2 diabetes.

At this time there are no means for preventing type 1 diabetes although there are numerous ongoing research studies trying to determine a means of identifying those at risk and once identified how to prevent its development.

Research is ongoing to find the cure of type 1 diabetes. Presently clinical trials are being conducted for islet cell transplantation. This research has progressed over the past 10 years and presently a small number of patients have been off insulin for 3 years. Insulin producing cells are harvested from cadaver pancreases and then injected into the portal vein near the liver. They attach themselves to the liver and begin to produce insulin. Patients however are required to take immune-suppressant therapy to prevent their body from destroying theses cells. Research is also exploring improved techniques in harvesting a larger quantity of insulin producing cells and protecting those cells without having to use the immune suppressant therapies presently being used. As all immune suppressants have a host of side effects. Various research projects are exploring the use of stem cells, and xenotransplantation to provide the large number of insulin producing cells needed to be available to treat all patients with diabetes.

Research is also seeking new methods of administering insulin; inhaled insulin is now in phase 3 clinical trials. This is a rapid acting insulin so the number of injections will be reduced individuals will still be required to take a long acting insulin injection.

Cost

The cost of diabetes is staggering and as our population ages and the rate of diabetes continues to grow so will the expense to treat this devastating disease and its complications. According to statistics published by the CDC the total cost of diabetes a year is $132 billion. This is further broken down into direct medical costs of $92 billion with $40 billion in indirect costs, reflecting money lost to disability, loss of work time and premature death. There is also the cost of loss of quality of life, to which no dollar sign can be attached. Diabetes is expensive, however if we do not invest funds into prevention programs to change behaviors and assist individuals to manage their disease the cost of health dollars and life will be staggering. As the epidemic of diabetes spreads to a younger population health care cost, the loss of productivity, disability will affect an entire generation. It is time to make a commitment to dedicate funds and resources to combat this horrific disease.

Questions for NIH from Chairman Steve Buyer
Subcommittee on Oversight and Investigations
Committee on Veterans Affairs
April 29, 2004
Hearing on VA Research on Alzheimer's Disease,
Parkinson's Disease, and Diabetes

Question:

What are the top ten priorities in research at the National Institute on Aging (NIA)?

Answer:

The National Institute on Aging's core mission encompasses the following overall research priority areas for it extramural grant program:

- Alzheimer's disease and the neuroscience of aging
- Age-related diseases
- Biology of aging
- Behavioral and social aspects of growing older

The following six specific research areas are the complementary priorities of the intramural research program:

- **Molecular and Cellular Biology:** *caloric restriction, cell cycle control, signal transduction, DNA repair, physiology, medicinal chemistry, gene regulation, immunosenescence, vascular biology*
- **Neuroscience:** *neurodegenerative diseases, drug design and development;neuronal cell biology*
- **Genetics:** *genetic determinants of aging, cancer genetics, image informatics, computational biology*
- **Behavioral Research:** *personality, cognition, and psychophysiology*
- **Clinical Research** *Cardiology, Oncology, Immunology, Neurology, Endocrinology*
- **Epidemiology:** *frailty, cognition, body composition, disability, molecular biomarkers of aging*

Question:

On page 24 of the NIA's 2001-2202 AD Progress Report, it talks about a 5 year Indiana University Medical School research team that followed 2,147 African-Americans in Indianapolis and 2,459 Yoruba in Ibadan, Nigeria, to see whether they developed dementia and AD. All the study participants were 65 and older. Two-thirds were female. All participants at both sites received the same examination, which included a structured interview, neuropsychological testing and a physical examination. Results indicated that in the US group, 3.24 percent per year developed dementia, including 2.52 percent per year who developed AD. In the Nigerian group, 1.35 percent per year developed dementia, including 1.15 per year who developed AD.

What do these findings tell us? Are the differences significant enough to warrant further study of these two populations?

I noted that a second phase of the study is planned using the same populations, which will focus on genetic factors and non-genetic factors, including cholesterol levels, body mass index, hypertension, and diabetes. When will this study begin?

Answer:

The Indianapolis-Ibadan Dementia Project demonstrated that the incidence rates for Alzheimer's disease and dementia are significantly lower in the Yoruba population in Ibadan, Nigeria than in African Americans. The second phase of the study has been funded after favorable scientific peer-review and has already begun. Completion is projected for December 2005.

The risk for AD in Americans is now known to increase dramatically with age with nearly half of all individuals over age 85 thought to be affected. [1] By comparing populations with similar AD genotypes, the Indianapolis-Ibadan Dementia Project may further contribute to our understanding of potentially modifiable non-genetic factors to help slow or prevent the alarming trend in AD incidence. A detailed description is provided in the attached study abstract.

[1] Data from the Alzheimer's Association. See also Ernst, RL; Hay, JW. "The U.S. Economic and Social Costs of Alzheimer's Disease Revisited." *American Journal of Public Health* 1994; 84(8): 1261 – 1264. This study cites figures based on 1991 data, which were updated in the journal's press release to 1994 figures.

Abstract: *DESCRIPTION (Adapted from the Applicant's Abstract): In the new application of the Indianapolis Ibadan Dementia Project, we are proposing to study intensively the risk factors which may explain the differences in incidence rates. As these risk factors are likely to be multiple, complex, involving genetic, environmental as well as genetic-environmental interactive influences, larger cohorts than those we currently possess will be required. We propose to enrich our current surviving cohort of 800 subjects in each site by recruiting an additional 2000 African Americans and 2000 Yoruba, 70 years and over, for a total of 2800 subjects at each site. With this enlarged sample we propose to measure ApoE genotypes and ApoE promoter haplotypes on all subjects in both cohorts. As exploration of site differences suggest that factors associated with increased vascular risk may be a productive line of investigation, we will also measure a number of biochemical values known to be associated with cardiovascular risk. We will continue to collect our current clinical, neuropsychological and socio-demographic data. With these new data we propose to test the following hypotheses. 1) Possession of the e4 allele of ApoE will be a stronger risk factor for AD in African Americans than in the Yoruba. The ApoE 2 allele will be protective for AD in the African Americans but not in the Yoruba. 2) Vascular risk factors increase the risk of dementia, AD and cognitive decline within each population site. The lower prevalence of these factors accounts for some of the differences in rates of AD and dementia between sites. 3) The interaction between ApoE genotypes and vascular risk factors alter the strength of the association between the ApoE 4 and 2 alleles and AD and account for some of the variation in AD rates between the populations. Our secondary aims are, 1) to continue to develop measurements of social engagement and activity levels which can be applied validly across sites; 2) to continue to evaluate natural history of cognitive and social functioning in two community-dwelling cohorts and to identify factors which may predict decline in cognitive and social function; 3) to determine if ApoE promoter haplotype is a risk factor for AD and correlate this risk with promoter transcriptional activity; and 4) to store blood, plasma and DNA samples for future genetic and biological studies.*

Questions for NIH from Chairman Steve Buyer
Subcommittee on Oversight and Investigations
Committee on Veterans Affairs
April 29, 2004
Hearing on VA Research on Alzheimer's Disease,
Parkinson's Disease, and Diabetes

Question:

What are the top ten research priorities at NIH?

Answer:

Determining research priorities is a complex, multifaceted process. One cannot easily quantify the various factors and questions that surround priority setting at NIH.

NIH's mission is to conduct research that will lead to better methods of diagnosing, treating, preventing and curing disease. NIH supported research has resulted in improvements in detecting disease, better therapies, and more effective vaccines.

We remain committed to the support of basic biomedical research. The investments NIH has made in biomedical research for cancer, the neurosciences, women's health, and pediatrics, has lead to longer and better lives. Our commitment to sustaining research in Cardiovascular disease – research identifying risk factors and new therapeutic interventions to control the risks were largely responsible for a dramatic reduction in mortality from stroke and heart disease over the last half century – will result in more saved lives over the next 50 years. And while we have come very far, we have even farther to go.

In short, NIH's research priorities are shaped by the need to better understand the smallest element of human biology, which leads us to the cause of disease, and ultimately a path toward treatment. At the same time, our priorities must reflect the evolving needs of the population we serve.

- Our newest priority is the NIH Roadmap which is a modest attempt at progress. The Roadmap is focused on three goals: Identifying new pathways of discovery; Building the research teams of the future; and Re-engineering the Clinical Research Enterprise.
- NIH is increasingly targeting chronic diseases.
- We have been responding to a new epidemic – obesity.

- We have been expanding our research efforts to protect the nation against bioterrorist threats.

- The NIH has an ongoing commitment to infectious disease research, such as AIDS, SARS, tuberculosis, malaria and influenza.

- The focus on vulnerable populations and rare diseases is also central to NIH's mission, and a component in priority setting.

- We remain committed to research on other long-standing problems, such as the health disparities that exist among racial, ethnic, and disadvantaged populations.

- Since the sequencing of the human genome, we are moving forward with research into molecules and proteins to gain knowledge leading to new therapies that will alter the way medicine is practiced.

As the most influential force in the U.S. biomedical research community, NIH exercises its leadership by continually surveying public health needs and the scientific landscape to identify new biomedical research areas that require attention. Simultaneously, we search for emerging scientific opportunities.

Our processes for identifying priorities and ensuring sound science have worked well. But reassessment and adaptation should occur and lead to a priority setting process that has greater public input, is more transparent, and lead to a research portfolio that will keep NIH at the leading edge of biomedical research.

Questions for the Record
Honorable Steve Buyer
Subcommittee on Oversight and Investigations
Committee on Veterans Affairs
April 28, 2004

Hearing on VA Research on Alzheimer's disease, Parkinson's disease and Diabetes

Question 1: On September 19, 2002, the Subcommittee on Oversight and Investigations held a hearing on VA research and research foundations. The Under Secretary was asked how many of the affiliated universities had signed Cooperative Technology Administration Agreements (CTAAs). At that time, the Under Secretary Roswell stated that notable universities such as Yale, Duke, Emory, and the University of Michigan had not signed such agreements.

Please provide the Subcommittee with the current status of these negotiations with these universities and all other affiliated universities engaged in collaborative research.

Response: VA has executed 60 CTAAs with many of the leading research institutions in the country, including Yale, Harvard, Stanford, and the entire University of California, Texas, and New York state systems to name a few. To date, the agreements have been extremely efficient in handling jointly owned intellectual property, and we have not encountered any substantive problems. VA continues CTAA negotiations with New York University, the University of Michigan, the University of South Florida, and the University of Pennsylvania in an effort to formally execute the agreements. Duke University contacted VA on April 27, 2004, and VA met with representatives from that institution on May 13, 2004. VA is awaiting a revised draft agreement from Duke. Several years ago, VA entered into discussions with Emory University about a CTAA. However, Emory had concerns with conditions of the agreement and did not want to pursue it.

Question 2: The VA testified that 1 in 6 veterans has diabetes and this accounts for nearly twenty five percent of all VA pharmacy costs and more than 1.7 million hospital bed days of care annually. The VA stated that diabetes affects nearly twenty percent of veterans receiving care in the VA and is the leading cause of complications such as blindness, end stage renal disease, and amputations. Furthermore, middle-aged persons with diabetes have 2 to 4 times the risk of coronary artery disease and stroke compared to similar persons without diabetes.

Why is it that VA only dedicates 4.6% of its research budget to diabetes?

Response: Attempting to link budgets to patient population percentages is problematic because many veterans have multiple diagnoses. First priority for VA-controlled funds goes to medical conditions that are unique to veteran populations. In addition, research in some conditions, such as diabetes, is more advanced than in others, thereby requiring full VA funding. VA research also attracts and retains clinicians in many disciplines, therefore, allocating funds based on patient populations would likely result in vacancies in hard to fill specialties. Another factor affecting VA funding decision is the ability to leverage non-VA funding. For example, National Institutes of Health (NIH) funding for diabetes research is nearly twice VA's entire research budget, thus permitting VA to focus assets elsewhere. As a result, VA cannot establish a direct relationship between percentage of budget resources devoted to diabetes research and the percentage of patients with diabetes.

What is the funding level (total dollars) from NIH to the VA for Alzheimer's, Parkinson's and Diabetes research?

Response:

	Alzheimer's	Parkinson's	Diabetes
NIH Funding (FY 03)	$36,443,338	$4,588,495	$24,551,412

What is the funding level (total dollars) from pharmaceutical companies to the VA for Alzheimer's, Parkinson's and Diabetes research?

Response:

	Alzheimer's	Parkinson's	Diabetes
Pharmaceutical Funding (FY 03)	$1,790,475	$558,379	$4,161,948

Question 3: How have veterans directly benefited from VA research on Alzheimer's, Parkinson's, and diabetes research? What are the measurable outcomes in terms of VA education for health care providers, new clinical practice guidelines, caregiver education, and support systems?

Response: VA research often results in direct tangible benefits to its veteran population. Examples in Alzheimer's, Parkinson's, and diabetes include:

Alzheimer's Disease

- Investigators are working to develop non-invasive techniques, including the identification of biomarkers, for early detection of Alzheimer's disease prior to the onset of severe memory loss or other cognitive deficits. In

addition, investigators are working with imaging technologies to discover ways to easily monitor the disease progression and response to therapy.

- Researchers are currently involved in a project to develop an Alzheimer's disease vaccine, and are also examining the potential of other pharmaceutical interventions.
- In June, two projects examining new potential treatments for Alzheimer's disease will be reviewed for FY 2005 funding. One project examines the efficacy of an herbal supplement component reported to be a memory enhancer and natural therapy for Alzheimer's disease. The other project examines two potential Alzheimer disease therapies, immunization/vaccine development and cholesterol lowering drugs (statins). Researchers have revealed a significant relationship between discomfort and agitation among nursing home residents with dementia, suggesting that agitated behaviors may be associated with increased pain. Accordingly, better quality of life for long-term care residents may result from regularly scheduled pain management.
- Researchers are working to help provide an environmentally safe home living situation for veterans with dementia by giving caregivers the knowledge and self-confidence to prevent risky behavior that leads to injuries.

Parkinson's Disease

- The Parkinson's Disease Research, Education, and Clinical Centers (PADRECCs) are implementing a prospective patient care registry as a means of monitoring the care of veterans. No such clinical Parkinson's disease registry has been previously established on a national scale. The anticipated benefits are the improvement of clinical care by tracking the clinical status and interventions of veterans with Parkinson's disease.
- State-of-the-art deep brain stimulation (DBS) technology to treat refractory Parkinson's disease has been shown to be an effective treatment in the short-term. Results from an ongoing VA collaborative research study will provide insight as to whether DBS is a superior treatment in the long-term to comprehensive medical therapy and whether greater effectiveness is associated with the site stimulated by DBS. More specifically, the study may help establish the optimal surgical treatment for disabling symptoms of Parkinson's disease and determine whether the treatment may cause long-term complications. In addition, as a result of the study, VA neurosurgeons have produced advances in the DBS surgical technique.
- The PADRECCs were also recently involved in a study to determine the indicators of quality health care for persons with Parkinson's disease. Using a literature review, followed by input from expert Parkinson's clinicians, a series of indicators were established, published and distributed system-wide in VA.
- The Associate Directors of Education work group has produced two telesatellite programs in conjunction with the Employee Education Service, the Telemedicine SHG, and the Geriatric Education Centers (GECs) (non-

VA/HRSA). The first telesatellite dealt with the use of telemedicine/telehealth in the care of veterans with Parkinson's disease. The second was a comprehensive educational program on Parkinson's. The latter has follow through of video and resource packets for wider distribution by the GEC at Virginia Commonwealth University.

- Investigators are working to identify biomarkers for early detection of Parkinson's disease, and are working with imaging technologies to discover ways to easily monitor progression of the disease.
- Researchers are utilizing body weight supported treadmill training to re-teach the body the proper gait patterns following trauma and during disease processes that compromise the ability to walk.
- Investigators are studying accelerated Transcranial Magnetic Stimulation to lessen depression and alleviate motor symptoms of Parkinson's disease.

Diabetes

- The combined efforts of many groups have produced significant improvements in VHA diabetes care and outcomes. Mean LDL cholesterol levels among veterans with diabetes dropped from 111mg/dL (FY 99) to 104 mg/dL (FY 01); VA patients' LDL-cholesterol levels are now equal to or better than those in the top 10% of all National Committee for Quality Assurance-accredited health plans. Similarly, the proportion of veterans with diabetes whose blood pressure is under control (less than or equal to 140/90) has increased from 43% in FY 1999 to 58% in FY 2002. VHA adherence to diabetes and non-diabetes indicators exceeded the average in Medicare Fee for Service in FY 2000 on 12 of 13 common indicators. Improvements in LDL levels and blood pressure control have been shown to lead to fewer cardiac incidents, strokes, and deaths. Based on changes observed in Veterans Integrated Service Network (VISN) 11 over a two-year time frame, we estimate an absolute reduction in risk of cardiovascular (CV) events and CV mortality of 6.5% and 4.4% respectively. If these results are applied to the approximately 10,400 veterans with diabetes in VISN 11 alone, CV events would be prevented for nearly 680 individuals over a 20-year period, and almost 460 lives would be saved.
- In FY 1996, the mean hemoglobin A1c value, a measure of average glycemic control, in VA was 8.3%, improving to 7.8% in FY 1998 and 7.4% in FY 2001. Simulation results suggest that a decrease in mean A1c from 8.2% in FY 1994 to 7.4% in FY 2001, as observed at some VA facilities, results in a 7 percent reduction in risk of blindness due to retinopathy.
- The Translating Research into Action in VA (TRIAD-VA) study, a collaboration between the Centers for Disease Control and Prevention (CDC) and VA, compared the quality of diabetes care between patients in VA and those enrolled in commercial managed care (CMC) organizations using equivalent and pre-specified sampling and measurement methods. Results show that diabetes processes of care were better for VA study

patients than for CMC patients, and that VA patients had better scores on 2 of 3 intermediate outcomes.

- Research from the Quality Enhancement Research Initiative for Diabetes Mellitus (QUERI-DM) suggests that VA Medical Centers with better coordination of foot care services (via tools such as pre-established plans, policies, procedures, information and communication systems to standardize work, and performance feedback such as report cards) have lower amputation rates. Over 92% of veterans have an annual visual foot examination, and about 84% a sensory examination. From FY 1999 - FY 2002, the age-adjusted rate of total diabetes related amputations performed in the VHA has decreased from 7.68 per 1000 veteran clinical users to 4.84. Major amputations decreased from 3.9 per 1000 veteran clinical users to 2.3; and minor amputations from 3.78 per 1000 veteran clinical users to 2.54.
- A large-scale clinical trial is ongoing to determine if intensified blood-sugar control and management reduces major vascular complications that lead to most deaths, illnesses and treatment costs for type-2 diabetic patients. Patients will receive either standard diabetic drug therapy or an enhanced, additive therapy regimen designed to maintain tight control over blood sugar levels. This study will be able to demonstrate the role of such intervention and have implications on the clinical care of the VA patient population (e.g., blood pressure control versus glucose control and the emphasis placed on such controls) in addition to determining the cost effectiveness/cost-benefit ratio of intensive treatment of diabetic patients.
- A joint Puget Sound VA Health Care System - University of Washington School of Medicine research initiative determined that a new antibiotic, linezolid, is as effective in treating antibiotic resistant diabetic foot infections. More important, linezolid can be delivered orally as well as intravenously, making it ideal for outpatient use. Foot infections are leading cause of diabetic-related hospitalizations and can result in amputation when infections fail to respond to therapy.
- A recent epidemiological study comparing auditory function in diabetic and non-diabetic veterans has shown that diabetic veterans 60 years of age or younger had significantly poorer hearing than non-diabetic veterans of comparable age. These findings suggest that diabetes may lead to premature aging of the auditory system, and that age-related hearing loss obscures differences over 60 years of age. These observations are likely to bring about changes in the standard of care provided to diabetic patients including routine hearing tests to reveal changes in hearing status, and offer opportunities for early intervention.
- Researchers are investigating the genetics of prediabetic traits in familial type-2 diabetes. Their observations indicate that pancreatic beta-cell dysfunction is an early, inherited defect that later leads to type-2 diabetes. These studies offer an important approach to understanding the early pathophysiology of type-2 diabetes and enhance the possibility for targeted intervention in high-risk individuals.

- Researchers have established that delivery of a metabolically responsive insulin transgene to the liver using adenovirus produces near normoglycemia in multiple rodent models of diabetes. They have recently developed a novel viral vector potentially capable of inducing transgene expression for years in animals and humans. The observations from the studies have potential for the advancement of insulin gene therapy for the treatment of millions of patients with diabetes.

Question 4: Please provide the Subcommittee with a list of VA's top five veteran's centric research priorities.

Response: The following is a list of VA's top five veteran's centric research priorities. Each of these areas is extremely important to the veteran population:

- Deployment Related Conditions (e.g. Gulf War Veterans' Illnesses, limb loss, traumatic brain injury, wound recovery and rehabilitation)
- Spinal Cord Injuries
- Neurodegenerative Diseases (e.g. Amyotrophic Lateral Sclerosis, Parkinson's Disease, Alzheimer's Disease)
- Post-Traumatic Stress Disorder (PTSD)
- Substance Abuse

Question 5: The VA testified that it has developed six Parkinson's Disease Research, Education, and Clinical Centers (PADRECCS) since FY 2001. Who is in charge of these centers? Who is responsible for prioritizing and coordinating initiatives to avoid replication or duplication of efforts?

Response: The Office of Patient Care Services controls the PADRECCs. The centers receive overall direction and guidance from the National Director for Neurology Program Office, part of Medical-Surgical Services. The National Director, Neurology Service, is responsible for prioritizing and coordinating the efforts of the PADRECCs. A PADRECC Coordinator in the National Director's office is responsible for the day-to-day management and coordination of activities.

Several mechanisms are in place to ensure coordination of efforts and to avoid duplication. Each Center has been assigned responsibility for care of veterans for a specific geographic area, so that each Center has its own "Sphere of Responsibility". Of great importance are several inter-center, intra-disciplinary workgroups. For example representatives from each of the Centers are on the workgroups for the Associate Directors of Education, the Clinical Coordinators, the Administrative Assistants, the Health Research Services Investigators, and the Registry Advisory Group, to name a few. These workgroups meet regularly by conference call. The PADRECCs' involvement ensures coordination and non-duplication of effort not only among centers but also within the VHA system. An initiative of the PADRECCs, the VA Parkinson's Disease Consortium, is working to coordinate care of movement disorders throughout the VHA system. The

Center Directors are regular attendees at national Neurology meetings. Inter-governmental agency coordination of scientific efforts is facilitated by an inter-agency collaborative group. Scientific coordination of the Deep Brain Stimulation Study is managed by the Office of Research and Development, Cooperative Studies Program.

CHAIRMAN BUYER TO DR. KUSSMAN

House Veterans' Affairs
Subcommittee on Oversight and Investigations
Hearing on VA Research on Alzheimer's, Parkinson's and Diabetes
April 28, 2004

Post-Hearing Deliverables

Question: Explain whether there is a Cooperative Research and Development Agreement (CRADA) for the deep brain stimulation (DBS) Cooperative Studies project. Also, provide the level of VA funding for the project.

Response: VA is currently negotiating and reviewing a Cooperative Research and Development Agreement (CRADA) with Medtronic, Inc., to ensure VA rights to any new intellectual property that may derive from the study. Medtronic, Inc. owns the rights to the stimulator, and VA is conducting a multi-site trial to determine the overall cost-benefit of the FDA-approved device. The CRADA will require Medtronic, Inc. to provide additional financial support for the study. VA will inform the Subcommittee when VA and Medtronic, Inc. execute the CRADA.

The seven-year cost of the program is $16.4 million (Fiscal Years 2001-2007). VA is funding $7.3 million, and the National Institute of Neurological Disorders and Stroke is providing the other $9.1 million.

Question: What are the performance measures associated with the MOVE project at the Durham VAMC?

Response: The Managing Overweight/Obesity in Veterans Everywhere (MOVE) is a national VA weight management/physical activity initiative, under development by the VA National Center for Health Promotion and Disease Prevention (NCP). It is presently being piloted at 17 VA medical facilities across the country.

Evaluation and performance measures associated with the MOVE project are currently under development. These measures include the following:

A. Formal assessment of the 17 pilots at mid-way and end points is being outsourced to an independent evaluator.

- Pilot assessments will focus on effectiveness of materials provided to clinicians and veterans, and implementation factors affecting facility resources and optimal patient flow.
- Results will help determine optimum patient processing and patient flow as well as future material and resource needs at VA medical facilities. Completion of data analysis reported is projected for late 2004 or early 2005.

- The results of the pilot assessment will be used to guide the development of full deployment performance measures.

B. Upon full implementation of this initiative across VA, data collection and analysis of MOVE will be continual, with results guiding improvements to the program to maximize effectiveness, and add scientific insight to weight management as a national program.

- Performance measures and monitors will be extensive, given the scope of the project and this unusual opportunity to favorably affect weight and physical activity in almost 5 million overweight VA enrollees.
- Clinical practice recommendations and performance measures will be derived based on experience from the pilots, on-going data analysis, and in accordance with VHA Office of Quality and Performance policy guidelines.

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